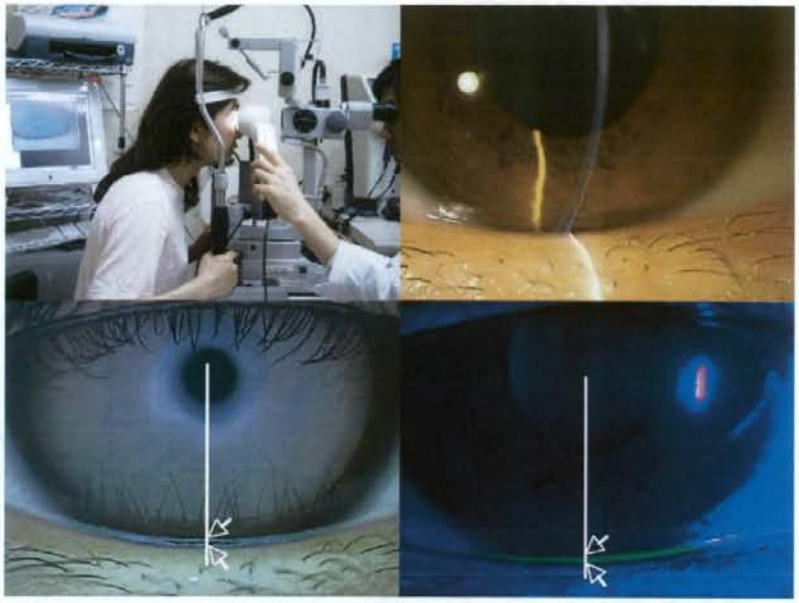

FIGURE 1. Measurement of noninvasive tear meniscus height (NI-TMH) using Tearscope Plus. (Top left) Tearscope interference device is set between the subject's eye and the slit-lamp. Precorneal tear interference image and tear meniscus interference image could be observed through the slit-lamp, and was recorded to the computer through the mounted digital video camera. Tear interference image with meniscus could also be seen on the computer screen. (Top right) Slit-lamp image of tear meniscus with diffuser light is shown. Tear meniscus of the same subject in Top left image is noninvasively visualized (Bottom left) and is also visualized with fluorescein staining (Bottom right). (Bottom left) Using image analysis software, the height of noninvasively visualized tear meniscus (between upper and lower white arrow) in central area (vertical white line) was measured. NI-TMH was quantified as 0.21 mm. Note that surface lipid layer of both tear meniscus and precorneal tear film is visualized by the tear interference device. (Bottom right) Using image analysis software, the height of fluorescein stained tear meniscus (between upper and lower white arrow) in central area (vertical white line) was measured in the same image capturing system. Fluorescein-stained tear meniscus height was quantified as 0.24 mm.

METHODS

• MEASUREMENT OF NONINVASIVE TEAR MENISCUS HEIGHT USING TEAR INTERFERENCE DEVICE: Tearscope Plus tear interference device was attached to the slit-lamp (SL130, Zeiss, Jena, Germany, magnification fixed to 12 ×, Figure 1). The tear interference image of the lower tear meniscus could be observed noninvasively when focusing at the lower lid margin. The image was captured using a high quality digital video camera (SP-321, JFC Sales Plan Co, Tokyo, Japan) attached through the beam-splitter of the slit-lamp and recorded using an image capturing system (P4m/MaxFile, P4 Medic Co, Kobe, Japan) in 720 × 480 pixels sized JPEG format. NI-TMH was measured using the ImageJ 1.32 image analysis software (National Institutes of Health, Bethesda, Maryland, USA). None of the subjects received any eye drop instillations at least six hours before the measurement.

As NI-TMH measurement with Tearscope Plus device has not been reported, it was compared concomitantly with conventional f-TMH in 31 eyes of 16 subjects. Nine eyes of five dry eye patients with SS (five females, mean age, 64 ± 8 years) and 22 eyes of 11 normal subjects (five males and six females, mean age, 34 ± 12 years) were measured. Initially, NI-TMH was measured with the Tearscope Plus tear interference device. Then, f-TMH was measured one minute after instillation of 2 μl of fluorescein solution with a micropipette. The images of NI-TMH and f-TMH were recorded and measured using exactly the same set-up as described above. The mean NI-TMH was 0.20 ± 0.09 mm, and f-TMH was 0.26 ± 0.11 mm. Images of the representative cases of NI-TMH and f-TMH are shown in Figure 1. The correlation between NI-TMH and f-TMH was also calculated with linear regression analysis. A significant correlation was found between NI-TMH and f-TMH ($r = .79$, $P < .0001$).

• SUBJECTS AND ASSESSMENT OF TEARS AND OCULAR SURFACE: We examined a consecutive series of 27 dry eye patients with SS (46 eyes, all female, mean age, 62 ± 10 years), as well as 17 normal subjects (28 eyes, all female, mean age, 52 ± 16 years). SS patients were diagnosed

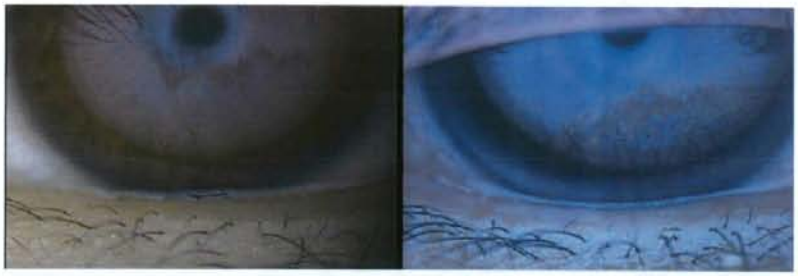

FIGURE 2. Noninvasive tear meniscus height (NI-TMH) between normal subjects and dry eye with Sjögren syndrome (SS). (Left) NI-TMH of a representative normal subject (0.28 mm). (Right) NI-TMH of a representative dry eye subject with SS (0.094 mm).

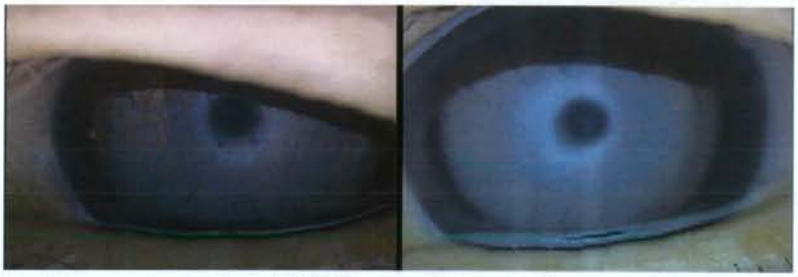

FIGURE 3. Noninvasive tear meniscus height (NI-TMH) before and after punctal occlusion. (Left) NI-TMH of a representative dry eye patient with Sjögren syndrome (SS) before punctal occlusion (0.17 mm). (Right) NI-TMH after punctual occlusion of the same patient (0.56 mm).

according to the criteria of Fox and associates.[27] Among the SS patients, eyes with a Schirmer I test value less than or equal to 5 mm were included in the study as they were considered to have ATD dry eye according to the Japanese dry eye criteria.[28] Eyes with a history of punctal occlusion, conjunctivochalasis, corneal transplantation, or corneal perforation were excluded from the study. In addition, eyes with anterior blepharitis and infectious conjunctivitis were also excluded. No patients used contact lenses in this study.

NI-TMH was assessed as described above before any invasive procedure. After that, the cornea was examined by fluorescein staining. A 2-μl volume of preservative-free solution consisting of 1% fluorescein dye was applied to the conjunctival sac. The intensity of the actual fluorescein staining of the cornea such as superficial punctate keratopathy was rated from a minimum of zero to a maximum of three, in each upper, middle, and lower cornea. Thus, the maximum total staining score was 9.[29] Tear film break-up time (BUT) was measured three times, and the measurements were averaged.[29] 2 μl of preservative-free solution consisting of 1% Rose Bengal dye was then applied to the conjunctival sac. The intensity of rose bengal staining in the cornea and conjunctiva was recorded, with the maximum score rated as nine points.[30] The Schirmer I test was then performed to measure the tear secretion volume.[31] NI-TMH was compared between dry eye subjects and normal controls.

• CHANGE OF TEAR MENISCUS HEIGHT AFTER PUNCTAL OCCLUSION: All dry eye patients received treatment with non-preserved artificial tears, and 0.1% non-preserved hyaluronic acid eye drops as necessary for at least two months. These subjects who were refractory to this treatment protocol underwent punctal occlusion. NI-TMH was compared before and three weeks after punctal occlusion or punctal plug insertion for both superior and inferior puncta in 11 eyes of eight subjects in an additional interventional case series (eight females, mean age, 69 ± 8 years). Flex plugs (Eagle Vision, Memphis, Tennessee, USA) were used for punctal occlusion in three eyes of three subjects, and punctal cauterization using Optemp 2 (Alcon, Fort Worth, Texas, USA) was performed in eight eyes of five subjects. Tseng's method was performed in punctal occlusion surgery[32] and the operation was successful in all cases without re-canalization.

• STATISTICAL ANALYSIS: All data are shown as means ± standard deviation. The Mann-Whitney *U* test was applied to the comparison of NI-TMH, fluorescein staining, rose bengal staining, tear film BUT, and Schirmer I test between SS and normal subjects. Wilcoxon matched pairs

test was applied to the comparison before and after punctal occlusion at each examination. A level of $P < .05$ was accepted as statistically significant. Graphpad Instat 3.0 (Graphpad Software Inc, San Diego, California, USA) was used for statistical analysis.

RESULTS

THE MEAN NI-TMH IN NORMAL SUBJECTS WAS 0.22 ± 0.065 mm. On the contrary, it was significantly lower (0.13 ± 0.042 mm, $P < .0001$) in dry eye patients with SS. The representative cases are shown in Figure 2. Corneal fluorescein staining mean score was significantly lower (0.46 ± 0.64) in normal subjects compared to dry eye patients with SS (4.0 ± 2.1, $P < .0001$). Rose Bengal staining mean score was significantly lower in normal subjects (0.18 ± 0.48) compared to dry eye patients with SS (4.6 ± 1.8, $P < .0001$). Similarly, tear film BUT was 5.9 ± 3.0 seconds in normal subjects, and it was significantly longer than in dry eye patients with SS (2.3 ± 1.4 seconds, $P < .0001$). Schirmer I test result was 13.9 ± 9.4 mm in normal subjects, and it was significantly longer than in dry eye patients with SS (1.7 ± 1.5 mm, $P < .0001$).

Images of NI-TMH before and after punctal occlusion in the representative case are shown in Figure 3. The mean NI-TMH significantly increased from 0.12 ± 0.026 mm to 0.42 ± 0.21 mm after the punctal occlusion procedure ($P = .001$). NI-TMH was increased after both punctal cauterization or punctal plug insertion procedures. In addition, corneal fluorescein staining mean score significantly decreased from 4.5 ± 2.3 to 0.27 ± 0.65 ($P = .002$), tear film BUT was prolonged from 0.91 ± 0.30 seconds to 5.2 ± 2.8 seconds ($P = .001$) and the Schirmer I test result increased from 2.8 ± 2.0 mm to 6.8 ± 4.2 mm ($P = .005$). On the contrary, Rose Bengal staining mean score decreased, but not significantly, from 5.0 ± 1.7 to 2.5 ± 2.0 ($P = .06$).

DISCUSSION

IN THE PRESENT STUDY, USING THE TEAR INTERFERENCE device, tear meniscus was successfully visualized in a noninvasive manner in all cases. We showed that NI-TMH measurement could be as relevant as the conventional f-TMH measuring method in the diagnosis of dry eye syndromes, could differentiate between normal subjects and ATD dry eye patients with SS, and could help in the evaluation of the change of meniscus height after punctal occlusion.

NI-TMH was significantly lower in dry eye patients with SS (0.13 ± 0.042 mm) compared with normal controls, (0.22 ± 0.065 mm) along with higher fluorescein and rose bengal staining, shortened tear film BUT, and lower Schirmer I test result. After punctal occlusion, NI-TMH significantly increased from 0.12 ± 0.026 mm to 0.42 ± 0.21 mm along with the improvement of corneal fluorescein staining, tear film BUT, and Schirmer I test result. NI-TMH was increased after both punctal cauterization or punctal plug insertion procedures. We believe that NI-TMH accurately reflects the deficiency of tear volume on the ocular surface in ATD dry eye patients with SS.

The values of NI-TMH in this study are low compared with the previous studies on TMH.[9,11–15,33] The previous data related to TMH mainly measured with fluorescein dye. In this study, a significant correlation was found between NI-TMH and f-TMH, and NI-TMH was slightly lower than f-TMH. This was possibly because of the addition of a minimal amount of water added to the fluorescein dye. The other merit of the present method is visualization ability even when the TMH is very low. In a previous study, using direct observation of the TMH with the slit-lamp, Oguz and associates reported that tear meniscus could not be observed when it was too low in dry eye subjects.[10] Our method using interference phenomena could visualize clearly such low tear meniscus even in ATD dry eyes with SS (Figures 2 and 3). Furthermore, in the principle of tear interferometry, reflectance is ranged approximately from 2% to 6%.[17,18,34] Thus, tear interference image of tear meniscus could be visualized even in dry eye cases with lipid tear deficiency. Using optical coherence tomography in ATD dry eyes, Savini and associates recently reported that mean NI-TMH was significantly lower in patients with ATD dry eyes (0.13 ± 0.07 mm) than in the control group (0.25 ± 0.08 mm).[35] We considered that their results strongly support the relevance of our method.

Compared with fluorescein-stained tear meniscus observation, noninvasive tear meniscus observation using the interference device has one demerit in terms of the limitation in the observation area. As shown in the figures, this method could visualize frontal tear meniscus at a limited observation angle. To observe all lower and upper tear meniscus areas from the inner to outer canthi, we considered that the fluorescein staining method still has some advantages.

Recently, another tear meniscus measuring device to measure meniscus radius curvature has been reported by Yokoi and associates.[36,37] This noninvasive method, however, is not widely available yet, and we chose the Tearscope interference device for the evaluation of tear meniscus in this study. Furthermore, height and radius of tear meniscus have been reported to have a positive correlation by Yokoi's group.[10] Thus, we also believe that the measurement of the NI-TMH is important, as well as tear meniscus radius measurement.[38]

In this study, we compared NI-TMH of normal and dry eye patients with SS who are representing ATD dry eyes. In the future, NI-TMH measurement of the other dry eye subtypes such as non-SS dry eye, meibomian gland dys-

function,[39] or dry eye with only decreased tear film BUT[40] would be highly anticipated. Furthermore, observation of the upper NI-TMH using Tearscope in superior limbic keratoconjunctivitis,[41] or lid-wiper syndrome[42] would be also interesting.

As many clinicians are aware, the diagnosis of ATD dry eyes is sometimes difficult owing to the variability of the Schirmer I test results by its invasive nature. In the future, we expect that NI-TMH measurement by the tear interference device would become an established tear volume evaluation test such as the Schirmer I test.[31]

In conclusion, NI-TMH measurement using the tear interference device could be considered to have similar clinical relevance compared with conventional f-TMH measurement. Not only did this method evaluate tear aqueous volume noninvasively, but it could also indicate significantly lower NI-TMH in ATD dry eye patients with SS and, was useful for indicating the increase of NI-TMH after the punctal occlusion procedure. The difference of NI-TMH in normal and dry eye groups was considered to reflect the difference of tear volume, which is responsible for moistening and maintaining the ocular surface.

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OPTOMETRY AND VISION SCIENCE

CASE REPORT

Management of Evaporative Dry Eye in Ectrodactyly-Ectodermal Dysplasia-Clefting Syndrome

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ABSTRACT

Purpose. The purpose of this study is to report the features of dry eye and ocular surface disease in an unusual case of ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome.

Case Report. A single observational case report of a 22-year-old Japanese male with evaporative dry eye and corneal epithelial disease because of lipid layer abnormality resulting from meibomian gland agenesis was treated successfully with low dose lipid base ointment application.

Discussion. The clinical features of the dry eye and ocular surface disease and management issues are discussed.

Conclusion. Low dose lipid base ointment application may be a promising treatment modality for the ocular surface disease in ectrodactyly-ectodermal dysplasia (EEC)-clefting syndrome, which seems to help in alleviating the subjective complaints and in improving the objective clinical findings.

(Optom Vis Sci 2008;85:E795–E801)

Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome is a rare autosomal dominant disorder, which is characterized by clefting deformity of the hands and/or feet (ectrodactyly-lobster claw deformity), ectodermal dysplasia, and cleft lip with or without cleft palate with at least two of the three cardinal features needed for diagnosis.[1–5] The features of ectodermal dysplasia include hypopigmented skin and hair, dystrophy of the nails, abnormal teeth, and lack of sebaceous glands.[1,2] Other systemic problems consist of urinary tract abnormalities, inguinal hernia, conductive hearing loss, and mental retardation.[1] In relation to the genetics of this rare disorder, variable expressivity is common in EEC syndrome families. A survey of 230 cases from the literature found that ectrodactyly occurred most often (84%), followed by ectodermal dysplasia (77%), and facial clefting (68%).[6] Genetic heterogeneity also exists, as EEC has been mapped to more than one chromosomal location: EEC1 on chromosome 7q11.3-q21.1,[7,8] EEC2 on chromosome 19,[9] and EEC3 on 3q27.[10] The single family that mapped EEC2 to chromosome 19 also showed linkage to 3q27, so it is possible that the EEC2 localization is spurious.[10] A recent mutation screen of 43 unrelated individuals affected with EEC syndrome revealed that 40 (93%) had mutations at TP63 (EEC3), suggesting that this is the most common cause of EEC1. Interestingly, however, genetic changes at both the EEC1 and EEC3 locations can also produce nonsyndromic split hand/split foot malformation (SHFM).[7,11] The prevalence of this group of syndromes can only be estimated. The overall prevalence seems to be in the order of 100 per 1 million of population.[12] The Birth Defects Encyclopedia indicates seven patients with ectodermal dysplasia in 10,000 births. More than 150 different ectodermal dysplasia syndromes are registered. The most prominent forms among these are[12]: hypohidrotic ectodermal dysplasia, ectrodactyly-ectodermal dysplasia-clefting syndrome (EEC syndrome), hidrotic ectodermal dysplasia (Clouston syndrome), ankyloblepharon–ectodermal dysplasia–clefting syndrome (Hay–Wells syndrome), incontinentia pigmenti, anhidrotic ectodermal dysplasia–clefting syndrome (Rapp–Hodgkin syndrome), trichodentoosseous syndrome and tooth-and-nail syndrome (Witkop syndrome). The four most frequent syndromes among these are hypohidrotic ectodermal dysplasia, EEC syndrome, ankyloblepharon–ectodermal dysplasia–clefting syndrome, and hidrotic ectodermal dysplasia. This is also empha-

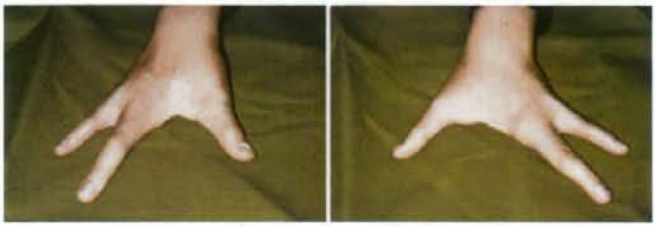

FIGURE 1.
Photograph of both hands of the patient showing signs of ectrodactyly-ectodermal dysplasia-clefting syndrome. Note the "lobster-claw deformity." Reprinted with permission from Springer Science and Business Media, Jpn J Ophthalmol 2004;4:373.

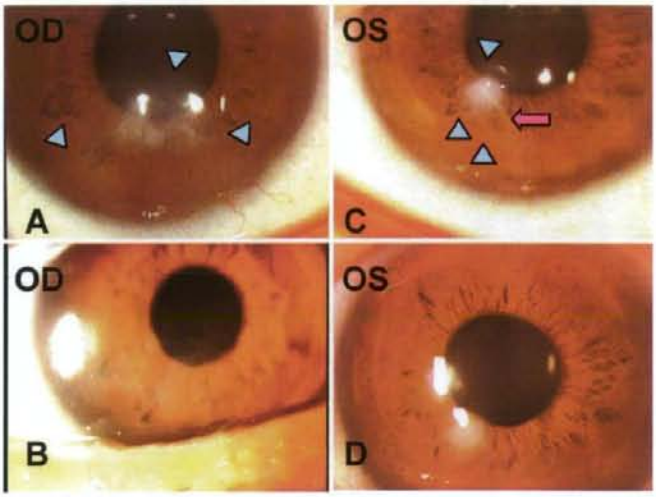

FIGURE 2.
Anterior segment findings before and after low dose lipid base ointment application. (A, B) Note the corneal opacification and vascularization in the right eye. The borders of the corneal haze and opacity extending into the pupillary area are depicted by light blue triangle tips. Note the regression of the haze and decrease in the density of the corneal opacity after treatment at the final visit. (B, D) Note the elevated corneal opacity with adjacent indentation in the pupillary area and the borders of the overall haze as depicted by the blue triangle tips and the pink arrow. Note the regression of the indentation, involution of the elevation and regression of the haze beneath the elevation, especially the area depicted by the pink arrow.

sized by the questionnaire results of the American self-help group for ectodermal dysplasia (www.nfed.org/nfedserv.htm). Patients with ectodermal dysplasia syndromes suffer above all from dental anomalies, dry skin, and dyshidrosis.

The reported ophthalmologic manifestations are strabismus, telecanthus, fused lids at birth, blepharophimosis, entropion, absence of eyelashes, bilateral eyelid cysts, agenesis of lacrimal puncta, dacryocystitis, blepharitis, conjunctivitis, meibomian gland dysfunction, and corneal limbal deficiency.[1–5] The ophthalmological problems are responsible for a wide variety of ocular surface disorders, such as recurrent corneal erosions, corneal opacification, vascularization, and perforation.[1–5] However, the cause of such ocular surface disorders in EEC syndrome is still unclear.[5] In 1995, Lemp reported that patients with absent or deficient meibomian gland function should be categorized in the evaporative group of dry eye syndromes.[13]

We hereby, report for the first time about the successful management of the ocular surface disease and evaporative dry eye resulting from lipid layer abnormality with low-dose lipid application on the full length eye lid margin in a patient with EEC syndrome who had agenesis of meibomian glands.

CASE REPORT

We describe a 22-year-old male Japanese patient with EEC syndrome, who had ectrodactyly-ectodermal dysplasia, lobster-claw deformity (Fig. 1) with no cleft lip or palate. At 4 years of age, he had a history of bilateral dacryocystorhinostomy because of congenital nasolacrimal duct obstruction. Systemic examination revealed hydronephrosis from congenital urinary tract abnormality, as well as hypopigmentation of his skin and hair. He had recurrent corneal erosions and ulcers from childhood, which resulted in corneal opacification and vascularization (Figs. 2A and C). Slit-lamp examination also showed the absence of meibomian gland orifices with hyperemia of the upper and lower eyelid margins, tarsal and bulbar conjunctiva (Figs. 3A to D). There were no clinical slit lamp findings or conjunctival culture evidence of keratoconjunctival infection in either eye. Apart from the ophthalmologically character-

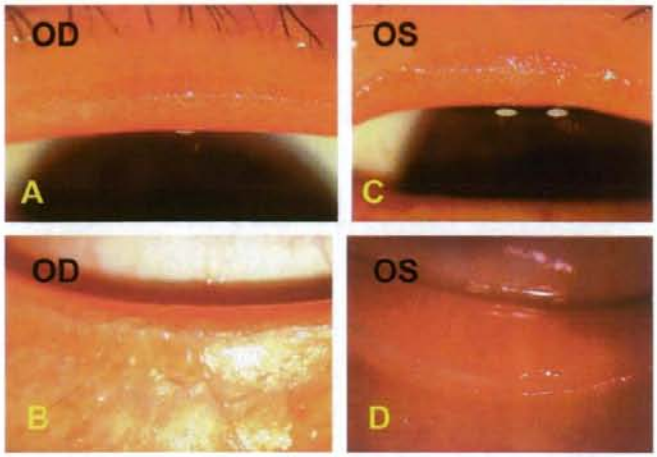

FIGURE 3.

Note the absence of meibomian gland orifices with hyperemia of the upper and lower eyelid margins, tarsal and bulbar conjunctiva in both right (A, B) and left (C, D) eyes.

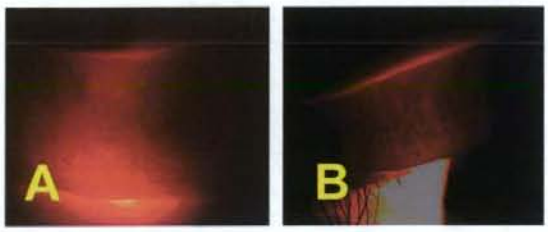

FIGURE 4.

(A) Note the absence of meibomian glandular structures during fiber optic probe transillumination of the eyelid. (B) Note the presence of glandular structures from an age matched normal control subject. Figure 4A reprinted with permission from Springer Science and Business Media, Jpn J Ophthalmol 2004;4:374.

istic features of EEC syndrome such as absence of meibomian glands (detected also by transillumination of the eyelids with a fiberoptic transilluminator at the first examination as shown in Fig. 4A with comparison to transillumination images from an age matched normal control subject in Fig. 4B, corneal scarring and vascularization in this patient, other features of this syndrome usually observable in the iris, lens or the retina, were not detected. The patient was on a prescription of unpreserved artificial tears six times a day and 0.1% vitamin A eye drops q.i.d., which the patient reported to have used without any problems for over 5 years. Because of the recent nature of his visual display terminal work requiring visual tasking for long hours, he started having complaints of severe burning, irritation, foreign body sensation, and conjunctival injection. He interestingly stated "degradation/blur of his vision when viewing a computer screen or reading a text without blinking" and that his vision became clear again with an intentional blink. He also reported worsening of the dry eye and visual symptoms especially during windy days, when exposed to coolers, cigarette smoke, and during air travel.

His best corrected visual acuities at the initial examination as of July 2006 were 20/20 OD -2.50×95 and 20/25 OS -4.00×60. Because of the aforementioned visual complaints, the patient underwent dynamic visual acuity testing with the Functional Visual Acuity (FVA) Measurement System (Nidek, Aichi, Japan), which is used to examine the time wise change in the continuous visual acuity as reported previously.[14,15] In brief, the optotypes were displayed automatically starting with smaller ones. If the responses were incorrect, larger optotypes were presented automatically. When there was no response within the set display times, the answer was supposed to be an error and the optotype automatically enlarged. Visual acuity was continuously measured for 60 s from the baseline best corrected Landolt visual acuity. The mean log MAR FVA value in both eyes were $+0.02 \pm 0.02$. The print out of the initial FVA testing is shown in Fig. 5A. Fluorescein staining of the cornea showed superficial punctate keratopathy in both eyes with a fluorescein staining score of 6 points out of a scale where the maximum corneal staining score was 9 points. Tear film break-up time (BUT) was 0 s in both eyes. The results of Schirmer I test was 24 mm OD and 10 mm OS. Tear film lipid layer interference image (DR-1; Kowa, Tokyo, Japan) showed Grade 5 with an irregular tear film surface, numerous dry spots, and areas of corneal surface exposure[16] (Fig. 6A). We measured the tear evaporation rate with a quartz crystal humidity sensor with a fixed room temperature of 24°C and a room humidity of 30% each time. (Analytical Research Center, Kao, Tochigi, Japan).[17] The tear evaporation rate was elevated to 8.2×10^{-7} g/cm^2 per second OD and 7.6×10^{-7} g/cm^2 per second OS (normal: $4.1 \pm 1.4 \times 10^{-7}$ g/cm^2 per second).[18]

We also measured the kinetic tear stability by tear stability analysis system (TSAS), which was installed in the Topographic Modeling System (TMS-2N; Computed Anatomy, Tomey Technology, Tokyo, Japan). In TSAS testings, 30 mire rings are projected on the corneal surface. The projected images are captured by videokeratoscopy. During TSAS measurements, corneal topograms were taken every second for 10 s after opening the eyes as previously described by the authors.[19] Eleven consecutive images were displayed on one printout. TSAS measurements during the initial examination revealed persistent tear surface

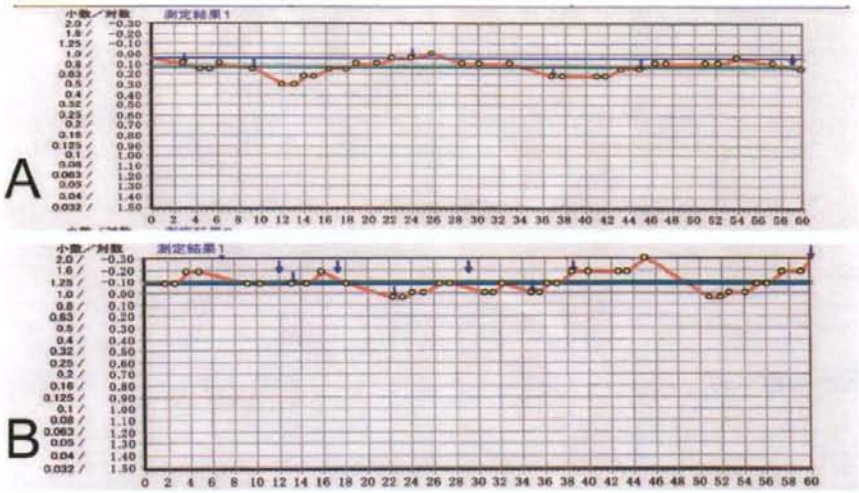

FIGURE 5.

Functional visual acuity testing before and after treatment. (A) Blue line indicates the starting best corrected Landolt visual acuity level. Green line indicates the mean functional visual acuity level attained during the 60 s testing. Arrows indicate blinks and yellow circles indicate the correct responses (B) Note the improvement of the mean functional visual acuity shown by the elevation of the green line to the blue line level after treatment.

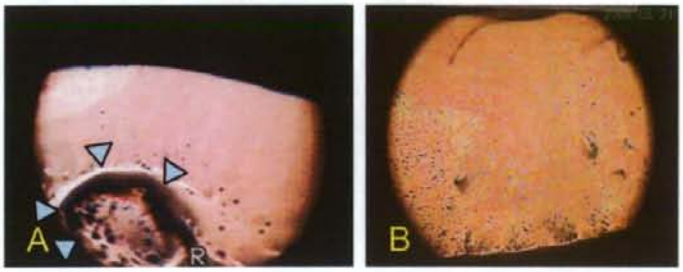

FIGURE 6.

DR-1 tear film lipid layer findings before and after treatment. (A) Tear film lipid layer interference image before treatment showed an irregular tear film surface, numerous dry spots and areas of corneal surface exposure (blue triangle tips). (B) Note the attainment of corneal surface regularity and disappearance of corneal exposure with lipid surfacing derived from the ointment base over the tear film. Figure 6A reprinted with permission from Springer Science and Business Media, Jpn J Ophthalmol 2004;4:374.

irregularity in both eyes (Figs. 7 A and C). All these testings were performed between 10.00 a.m. and 12.00 p.m. in the morning at all follow-up visits approximately 4 to 5 h from the last low-dose application of the lipid base ointment.

We diagnosed the patient as having evaporative dry eyes because of tear film lipid layer deficiency and treated the ocular surface disease by showing the patient application method of 0.05 g of ofloxacine ointment along a length of 2 mm on a glass rod using a calibrated grid and then spreading the ointment on the full-length lower eyelid margin to distribute the lipid as a uniform layer over the ocular surface as reported by Goto et al. previously.[20] The low-dose ofloxacin eye ointment application on the eyelid margin was carried out twice a day by the patient (once before bed time and once after waking up in the morning) for 4 week initially and then throughout the follow-up in addition to the preexisting treatment.

The patient's symptoms resolved completely within a month. The follow-up visit as of August 2006 revealed tear film break up times of 6 s OU, with a decrease in tear evaporation grades to 6.8×10^{-7} g/cm^2 per second OD and 5.7×10^{-7} g/cm^2 per second OS. Fluorescein staining scores had decreased to 3 points OD and 1 point OS by then. At the 12th month follow-up visit, no corneal epithelial erosions were noted. Slit lamp microscopy revealed regression of corneal haze and reduction in the density of corneal opacities with treatment (Figs. 2B and D). BUT values were still prolonged at 6 s in each eye at the final examination. Schirmer I test values were 15 mm OD and 10 mm OS. Best corrected Landolt visual acuities at the final examination were 20/25 OD with a refraction of +0.5D -2.5×95 and 20/25 OS with a refraction of -3.5×75 and with the mean log MAR FVA showing improvement to -0.09 ± 0.01 (Fig. 5B). Tear evaporation rates after treatment were 4.2×10^{-7} g/cm^2 per second OD and 5.4×10^{-7} g/cm^2 per second OS. DR-1 tear film lipid layer interferometry showed attainment of corneal surface regularity and disappearance of corneal exposure with lipid surfacing over the film derived from the ointment base (Fig. 6B). TSAS examination after treatment also showed attainment of tear surface regularity and improvement of tear film break-up

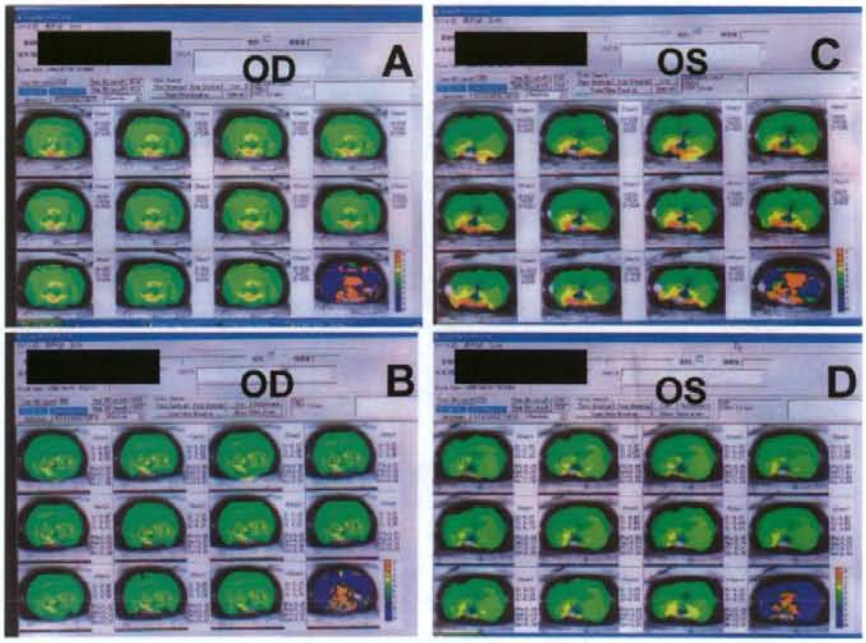

FIGURE 7.

Alterations of tear surface regularity assessed by tear stability analysis system before and after treatment. (A and C) Note the persistent tear surface irregularity in both eyes during a 10 s continuous testing by TSAS before treatment. (B and D) TSAS examination after treatment showed attainment of tear surface regularity and improvement of tear film break-up maps.

maps (Figs. 7B and D). No treatment related complications or adverse effects were observed during the follow-up.

DISCUSSION

The etiology of ocular surface disease in EEC syndrome remains unclear.[5] Possible explanations include: 1) infections such as chronic conjunctivitis and dacryocystitis[21,22]; 2) decreased or absence of lacrimal and meibomian gland functions[6,23]; 3) ectodermal dysplasia with a possible primary developmental defect in the corneal epithelium during embryogenesis.[24]

In our case, the tear quantity was normal although there was extensive tear instability in both eyes. The slit-lamp examination revealed the absence of meibomian gland orifices as well as absence of coexistent lid infections. Transillumination of the lids with a fiber optic probe also showed the absence of meibomian glandular structures. Tear film lipid layer interferometry has been shown to be effective in diagnosing and determining the severity of dry eye disease.[16] The interference grades have also been shown to correlate with tear film BUT and vital staining scores. DR-1 tear film lipid layer interferometry grade in our patient was a Grade 5 with an irregular tear film surface, numerous dry spots, and areas of corneal surface exposure. Thinking that the absence of meibomian glands would lead to a deficiency in the lipid layer, which is believed to retard the tear evaporation, we measured the tear evaporation rate, which was found to be considerably elevated compared with the previously published data from healthy control subjects ($4.1 \pm 1.4 \times 10^{-7}$ g/cm^2 per second; 12 female and 10 male; average age, 39.5 ± 9.5 years) or patients with obstructive meibomian gland dysfunction ($5.8 \pm 2.7 \times 10^{-7}$ g/cm^2 per second; 12 female and 9 male; average age, 46.0 ± 14.4 years).[18]

Mathers et al. reported that the tear evaporation rate was three times higher in patients with meibomian gland disease compared with that of normal subjects.[25] Iwata et al. similarly reported a 4-fold increase, whereas Mishima et al. noted a 10-fold elevation of the tear evaporation rates in rabbit models of marked or absolute tear film lipid deficiency compared with normal rabbits.[26,27] Although histopathological confirmation could not be obtained because of the patient's refusal of a diagnostic biopsy, our findings on the absence of a marked elevation of the tear evaporation rate in our case compared with other reports suggests the presence of some lipid in the tear film which calls for further relevant biochemical and histopathological investigation in EEC patients. Moreover, the tear evaporation rate was still higher compared to patients with obstructive meibomian gland dysfunction.[18]

Although a previous report by Lemp presumed that EEC syndrome belonged to the evaporative type of dry eyes,[13] our report provides evidence that increased tear evaporation was one of the important processes in the pathogenesis of dry eye and keratopathy in this rare syndrome. We previously treated this patient with vitamin A eye drops containing lipid components such as castor oil and vegetable oil to provide support to the ocular surface epithelium and the lipid layer of the tear film. This approach was observed to eliminate recurrence of corneal complications.[28] However, a change in working conditions which required him to carry

out long hours of visual display terminal work during weekdays for the last 2 month, in our belief, caused an additional evaporative stress on the ocular surface. Indeed, visual display terminal (VDT) work has been previously reported to be associated with greater tear evaporation and lipid layer abnormalities.[29] Increased tear evaporation and resultant tear instability might have caused resurgence of dry eye and visual symptomatology in the patient. Interestingly, DR-1 lipid layer interferometry and TSAS examinations confirmed the tear surface irregularity with DR-1 also revealing areas of corneal surface exposure. These changes were associated with a concomitant decline in functional visual acuities despite 20/20 best corrected Landolt visual acuities.

Recently, FVA testing has been reported to be an important method of defining "detailed visual function."[14,15] This method has been shown to be efficient in the detection of "masked impairment of visual function" in dry eye patients who complain of decreased visual acuity despite normal conventional visual acuity. The definition of FVA testing has been suggested to be an important indication of an individual's performance in relation to certain daily activities involving visual performance.

One possible treatment approach in VDT workers associated with evaporative dry eyes is topical lipid therapy. The bulk application of lipid drops or lipid based ointments can cause patients to complain of lengthy visual blur which may not be suitable for dry eye treatment, because in our experience, most patients expect an increase in visual acuity after treatment. For optimal dry eye lipid treatment, we reported in our previous study that it was important to apply a small quantity of lipids to achieve a uniform spread over the tear aqueous layer. The hydrophilic polar lipid is a key point for the lipophilic nonpolar lipid to form a uniform layer on water.[30] We chose to apply ofloxacine ointment (consisting of 0.3% ofloxacin, liquid paraffin, white petrolatum, and purified lanolin as its base) because currently, there are no Japanese Ministry of Health, Labor and Welfare approved topical lipid preparations for dry eye treatment in Japan. Therefore, the only way to deliver lipids for evaporative dry eyes in Japan is to use vitamin A, corticosteroid, or antibiotic ointments, which basically contain only a nonpolar lipid base. Moreover, ofloxacin eye ointment (Santen Pharmaceutical, Osaka, Japan) is the only nonpreserved antibiotic ointment that contains both polar and nonpolar lipids, making it suitable for the treatment of dry eyes.

First of all, this report provided important evidence into the actual decrease of tear evaporation rate after lipid application by the present method. The decrease of tear evaporation was associated with regression of corneal haze, and improvements in tear stability, tear surface regularity (as evidenced by tear film break up time, TSAS and tear film interferometry examinations), and corneal epithelial damage within a month after the initiation of treatment which we believe improved the overall ocular surface health. The favorable effects were maintained at the 1 year follow-up visit. One important point that we would like to stress in relation to tear evaporation and lipid interferometry measurements is that these parameters are subject to diurnal variations and the testings should be carried out under the same settings at each visit (fixed room temperature, humidity, and same time frames) just as we performed in this report.

Although continuation of the current treatment strategy throughout the follow-up was not associated with any adverse effects or recurrence of corneal epithelial disorders, it should be noted that long-term use of an antibiotic ointment may change the eye flora and result in emergence of antibiotic resistant strains. The use of a simple lipid base ointment is desirable in countries where such formulations are available. Although our case did not have coexisting blepharitis, we presume that cases with evaporative dry eyes due to obstructive meibomian gland disease and blepharitis might benefit from a short-term topical lipid base antibiotic ointment application which with eradication of blepharitis, should be replaced with simple lipid ointments or drops, in our opinion.

In conclusion, tear film instability caused by the absence of meibomian glands and lipid layer abnormality in EEC syndrome was thought to be associated with the ocular surface epithelial problems. We reported for the first time a promising treatment modality by low dose lipid application for the ocular surface disease in EEC, which helped in alleviating the subjective complaints and in improving the objective clinical findings.

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