Corneal Manifestations of Ocular Demodex Infestation

AHMAD KHEIRKHAN, VICTORIA CASAS, WEI LI, VADREVU K. RAJU, AND SCHEFFER C. G. TSENG

• PURPOSE: To report the corneal manifestations in eyes with Demodex infestation of the eyelids.

• DESIGN: Noncomparative, interventional case series.

• METHODS: This retrospective review included six patients with Demodex blepharitis who also exhibited corneal abnormalities, which led to suspicion of limbal stem cell deficiency in three cases. All patients received weekly lid scrubs with 50% tea tree oil and a daily lid scrubs with tea tree shampoo for a minimum of six weeks. Improvement of symptoms and corneal and conjunctival signs were evaluated.

• RESULTS: All six patients exhibited ocular irritation and conjunctival inflammation, while meibomian gland dysfunction (n = 5), rosacea (n = 4), and decreased vision (n = 3) also were noted despite prior treatments with oral tetracycline, topical steroids with antibiotics, and lid scrubs with baby shampoo. These patients were proven to have Demodex folliculorum (n = 6) and Demodex brevis (n = 3) by microscopic examination of epilated lashes. Their corneal manifestation included superficial corneal vascularization (six eyes of five cases), marginal corneal infiltration (two eyes of two cases), phlyctenule-like lesion (one eye of one case), superficial corneal opacity (two eyes of two cases), and nodular corneal scar (two eyes of two cases). After treatment, the Demodex count was reduced from 6.8 ± 2.8 to 1 ± 0.9 (standard deviation; P = .001). All patients showed dramatic resolution of ocular irritation, conjunctival inflammation, and all inflammatory, but not scarred, corneal signs; three patients showed improved vision.

• CONCLUSIONS: A variety of corneal pathologic features together with conjunctival inflammation, commonly noted in rosacea, can be found in patients with Demodex infestation of the eyelids. When conventional treatments for rosacea fail, one may consider lid scrub with tea tree oil to eradicate mites as a new treatment.

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The Demodex (Class Arachnid and Order Acarina) is a microscopic, obligate, elongated mite that is the most common permanent ectoparasite of humans. Among a wide range of reported species, only Demodex folliculorum and Demodex brevis are found on the human body surface and often coexist and tend to gather in the face, cheeks, forehead, nose, and external ear tract, where active sebum excretion provides a favorable habitat for breeding. In the eye, Demodex folliculorum is found in the lash follicle, whereas Demodex brevis burrows deep into the sebaceous gland of the eyelashes and the meibomian glands.

In the eye, Demodex infestation was thought to be linked to blepharitis and allergic blepharoconjunctivitis in a rosacea patient. Recently, we improved the method of sampling and counting these mites in epilated lashes and reported that Demodex infestation is highly correlated in patients with cylindrical dandruff in the lash roots. Furthermore, we discovered a new treatment based on a weekly lid scrub with 50% tea tree oil and daily lid scrub with tea tree shampoo to eradicate this mite infestation.

In a total of 11 patients with ocular demodicosis, we further reported that eight had conjunctival inflammation, seven showed meibomian gland dysfunction manifesting abnormal lipid film with slow lipid film spread, and five had intermittent trichiasis. However, in the realm of potential pathogenicity of ocular demodicosis, it remains unclear whether the cornea also may be affected.

METHODS

This study was conducted at the Ocular Surface Center, Miami, Florida, and was approved by the Institutional Review Board of Baptist Hospital of Miami/South Miami Hospital, Inc, Miami, Florida, to review retrospectively the medical records of six patients proven to have ocular demodicosis while also demonstrating abnormal corneal findings at presentation. All of them had either diffuse or sporadic cylindrical dandruff at presentation, defined as scales formed as distinct cuffs, collaring the lash root as previously reported. Ocular demodicosis was confirmed by microscopic examination of epilated lashes according to a modified method reported recently. Briefly, under a slit-lamp biomicroscope at a magnification of ×25, two lashes with cylindrical dandruff per lid were removed by fine forceps, were placed separately on each end of a glass slide, and were mounted with a separate coverslip. Under a light microscope for lashes without retained cylindrical dandruff, one drop of 20 μl saline were applied by a pipette to the edge of the coverslip, whereas for those with retained cylindrical dandruff, 20 μl of 100% alcohol (Sigma-Aldrich, St Louis, Missouri, USA) was

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## TABLE. Clinical Information of Patients with *Demodex* Blepharitis and Corneal Involvement

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Rosacea Symptoms</th>
<th>Uncorrected VA Before TTO</th>
<th>Demodex Folliculorum Before/After TTO</th>
<th>Demodex Brevis Before/After TTO</th>
<th>Conjunctival Inflammation* Before/After TTO</th>
<th>Corneal Findings Before/After TTO</th>
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<tr>
<td>1</td>
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<td>F</td>
<td>Yes</td>
<td>20/25</td>
<td>20/70</td>
<td>8/2</td>
<td>0/0 (both eyes) – (both eyes)</td>
<td>Periphera scar (both eyes), superficial vascularization</td>
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<td></td>
<td></td>
<td></td>
<td>20/40</td>
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<td>F</td>
<td>Yes</td>
<td>20/20</td>
<td>20/70</td>
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<td>0/0 (left eye) + (left eye) – (both eyes)</td>
<td>Nodular scar (left eye), peripheral scar (left eye)</td>
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<td>70</td>
<td>M</td>
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<td>20/20</td>
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<td>Central opacity (left eye), superficial vascularization</td>
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<td>20/20</td>
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<td>Phlyctenule-like lesion (left eye)</td>
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<tr>
<td>5</td>
<td>30</td>
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<td>20/20</td>
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<td>Superficial vascularization</td>
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<td>1/0</td>
<td>2/0 + + + (left eye) – (both eyes)</td>
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<td></td>
<td>20/30</td>
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*CD = cylindrical dandruff; F = female; M = male; MGD = meibomian gland dysfunction; TTO = tea tree oil; VA = visual acuity; FBS = foreign body sensation.

*Conjunctival inflammation was graded as + (mild), ++ (moderate), +++ (severe), or – (not present).*
added. For the former, the number of mites was counted immediately, whereas for the latter, the counting time was prolonged up to 20 minutes to allow the cylindrical dandruff to dissolve and to stimulate the embedded Demodex to migrate out. The Demodex count was recorded as a total number of mites found in a total of eight lashes and was compared after tea tree oil treatment using the paired t test.

Weekly lid scrubs with 50% tea tree oil and daily lid scrubs with tea tree shampoo also were advised for the patients for a minimum of six weeks, according to a regimen reported recently. The medical records, including the history of present illness, complete eye examination results, and external photographs, also were reviewed for the first visits and subsequent follow-up visits to compare the changes in subjective symptoms, objective ocular surface signs documented by external photography, and the Demodex count.

RESULTS

THESE SIX PATIENTS INCLUDED TWO WOMEN AND FOUR men, with an average age of 49.3 ± 17 years (standard deviation; range, 30 to 70 years). Demographic and other clinical features are summarized in the Table. All of them reported ocular surface irritation lasting several years. Their symptoms included redness (n = 5), blurred vision (n = 3), misdirected lashes (n = 2), vague ocular irritation (n = 1), ocular pain (n = 1), and recurrent chalazia (n = 1). Their symptoms persisted despite prior treatments including oral tetracycline, topical steroids with antibiotics, and lid scrubbing with baby shampoo for presumed blepharitis. Three of them (Cases 1, 2, and 4) had abnormal corneal findings that prompted the referring physicians to suspect limbal stem cell deficiency and had received superficial keratectomy and amniotic membrane transplantation without success. Their corneal lesions had recurred after surgery.

All patients had anterior blepharitis with cylindrical dandruff in their lashes at presentation, and the microscopic examination revealed Demodex infestation (Table). Notable was the finding that although Demodex folliculorum was found in all, Demodex brevis also was found in three cases (50%; Table). All of the patients also had notable conjunctival inflammation at presentation as evidenced by redness involving bulbar areas (six cases; see Figure 1, Top left, for an example) and tarsal areas (five cases). Five patients had meibomian gland dysfunction defined by plugging of the orifice, poor expression of the meibum on digital expression, or acinar dropouts on transillumination. Four patients had rosacea as evidenced by telangiectasia,
erythema, papules, pustules, and sebaceous gland hypertrophy in the flush areas of the face. Interestingly, conjunctival inflammation was severe enough to yield superficial corneal vascularization in six eyes of five cases (see Figure 1, Top middle, and Figure 2, Top left, for examples). In addition, other corneal manifestations included marginal corneal infiltration (two eyes of two cases; Figure 2, Top middle and right), a phlyctenule-like lesion (one eye of one case; Figure 2, Bottom left), superficial corneal opacity (two eyes of two cases; Figure 2, Bottom middle), and nodular corneal scars (two eyes of two cases; Figure 2, Bottom left and right; Table).

During a mean follow-up of 7.9 ± 7.7 months (standard deviation; range, one to 20 months) after weekly lid scrubs with 50% tea tree oil and daily lid scrubs with tea tree shampoo, the eyelashes became much cleaner with disappearance of cylindrical dandruff (not shown) consistent with our previous reports. The mean Demodex count was reduced from 6.8 ± 2.8 to 1 ± 0.9 (standard deviation; Table; P = .001). All patients also showed subjective improvement of ocular surface irritation and pain, with complete disappearance of conjunctival redness (Figure 1, Bottom left and middle) and regression of corneal superficial vascularization in all five eyes (see Figure 1, Bottom right, for an example). Nevertheless, intermittent trichiasis remained. Importantly, there was a marked improvement in the eye with a phlyctenule-like lesion and in eyes with marginal corneal infiltration (two eyes). Although the changes in corneal opacity and scar were not notable in three eyes, the visual acuity improved by 1, 3, and 4 Snellen lines in these eyes, respectively (Table).

**REPRESENTATIVE CASE REPORT:** Case 1. A 62-year-old woman was referred for being considered for limbal stem cell transplantation under the suspicion of limbal stem cell deficiency. She had reported ocular irritation, eyelid redness, conjunctival injection, misdirected eyelashes, and blurred vision in both eyes, especially in the left eye, despite several years of treatments for rosacea using oral doxycycline and topical prednisolone and loteprednol and topical antibiotics. Four months before the referral, her left eye had received superficial keratectomy and amniotic membrane transplantation for corneal opacity and peripheral corneal vascularization. However, nearly all corneal scarring and vascularization returned after surgery. On examination, her uncorrected visual acuity was 20/25 in the right eye and 20/70 in the left eye. Lid margins showed blepharitis with diffuse cylindrical dandruff, spo-
radic lash loss, trichiasis, meibomian gland dysfunction, and diffuse injection of tarsal and bulbar conjunctiva in both eyes (Figure 3, Top left and middle). Peripheral corneal scars with vascularization were noted in both corneas, with superficial central corneal opacity in the left eye with irregular fluorescein staining (Figure 3, Top middle and right). During the five-month follow-up after tea tree oil treatment, the patient’s symptoms were relieved significantly, her vision improved to 20/40 in the left eye, the conjunctival inflammation resolved (Figure 3, Bottom left), and most of the peripheral vascularization disappeared from the cornea with reduced fluorescein staining (Figure 3, Bottom middle and right). The Demodex count reduced from eight to two, and the impression cytologic analysis did not show conjunctivalization, that is, evidence of limbal stem cell deficiency, in either eye (not shown).

**DISCUSSION**

**DEMODEX INFESTATION IN THE FACIAL SKIN HAS BEEN implicated in causing rosacea**\(^{1,5,6,15,16}\) and in the eyelid in giving rise to blepharitis.\(^{7-10}\) Recently, we provided strong evidence supporting the notion that such blepharitis frequently is associated with mite-harboring cylindrical dandruff in eyelashes.\(^{12}\) Furthermore, we reported that 11 eyes with Demodex infestation in eyelashes also manifested trichiasis, meibomian gland dysfunction with lipid tear deficiency, and conjunctival inflammation.\(^{14}\) In this study, we also noted meibomian gland dysfunction, conjunctival inflammation, and trichiasis in these six patients with Demodex blepharitis. In addition, for the first time, they also had corneal manifestations at presentation that were serious enough to prompt the referring physician to suspect limbal stem cell deficiency in three cases. We also were surprised to note that among these six patients, all infested with Demodex folliculorum, three (50%) also were infested with Demodex brevis (Table). Our current clinical experiences disclosed that the chance of detecting Demodex brevis, normally thought to reside singly in the sebaceous and meibomian glands, in epilated lashes was rather rare in the general patient population, being approximately 9.1%\(^{12}\) (Tseng SCG, 2006 unpublished observation). Future studies are needed to determine whether such an unusually high infestation rate of Demodex brevis noted in this study may play a causative role in inducing these corneal manifestations.
Although Demodex has been implicated in facial rosacea, no study has shown whether mites also infest eyelashes in patients with ocular rosacea. Herein, we reported for the first time that four cases with facial rosacea also had ocular Demodex infestation. In patients with facial rosacea, the pathogenesis of skin lesions has been speculated to be caused by an increasing density of mites, which trigger inflammatory or specific immune reactions, mechanically block the hair follicle, or act as a vector to bring innate antigens derived from bacteria, viruses, protozoa, parasites, or fungi. Our results suggest that another potential foreign antigen may come from Demodex. Malign (catarrhal) corneal infiltration, if associated with a lucid interval from the limbus, is thought to be mediated by type III immune responses to exogenous staphylococcal or streptococcal antigens associated with blepharitis. Nevertheless, all four patients with rosacea had received oral tetracycline and topical steroids and antibiotics, that is, treatments recommended for ocular rosacea, without notable improvement of ocular manifestations. Therefore, we strongly suspect that immune dysregulation resulting from microbial (staphylococcal) infection, whether brought in by mites or not, may not be the likely cause.

In contrast, all six cases showed dramatic resolution of conjunctival inflammation after weekly lid scrubs with 50% tea tree oil and daily lid scrubs with tea tree shampoo. Furthermore, there was a significant reduction of mite counts (Table). These findings were consistent with our reports showing that 50% tea tree oil kills Demodex mites in vitro and in vivo and significantly reduced conjunctival inflammation in 11 cases with Demodex blepharitis. Moreover, our results further showed that lid scrub with tea tree oil also reduced such corneal manifestations as phlyctenule-like lesion and corneal infiltration and vascularization (Figures 1 and 3). Although the corneal opacities did not change significantly, the visual acuity improved in three eyes, presumably because of the increasing stability of the lipid tear film, as suggested in our recent report. Further investigation by impression cytologic analysis in Case 1 showed that the cornea was devoid of any sign suggestive of limbal stem cell deficiency after treatment.

Tea tree oil, a natural essential oil distilled from the leaf of Melaleuca alternifolia, has long been used as an aboriginal traditional medicine in Australia for wounds and cutaneous infection. Besides the antimite efficacy noted recently and in this study, tea tree oil also is known to exert antibacterial, antifungal, and acaricidal effects. Therefore, we could not absolutely attribute the aforementioned improvement of the patients’ symptoms only to the direct killing effect of tea tree oil treatment on Demodex mites. Although the subjective improvement of patients after treatment with tea tree oil may be influenced by the placebo effect, dramatic improvement in objective findings in the conjunctiva and the cornea has been documented in all patients by serial photography, of which the interpretation was not masked. Therefore, a prospective, randomized, clinical study with a larger sample size is warranted to resolve these issues.

REFERENCES
11. Morfin Maciel BM. Demodicidosis in a female patient


Biosketch

Scheffer C. G. Tseng, MD, PhD, after completing a residency at Johns Hopkins Hospital in 1984 and a cornea fellowship at Massachusetts Eye & Ear Infirmary in 1986, Dr Tseng had become a chaired professor at Bascom Palmer Eye Institute until 2002, when he assumed the medical director of Ocular Surface Center and Ocular Surface Research & Education Foundation, and R&D Director of TissueTech, Inc. Dr Tseng has been devoted to bridging clinical and basic research in ocular surface diseases and reconstruction.