CASE REPORT

Late-onset haze associated with chikungunya infection

Renato Correa Souza de Oliveira, MD, Tatiana Klejnberg, MD, Celso Klejnberg, MD, Mauro Campos, MD

A 42-year-old woman, who had undergone photorefractive keratectomy (PRK) 12 years earlier, complained of blurring of vision within 2 weeks of chikungunya infection. A central corneal stromal haze was observed in the left eye. Her corrected distance visual acuity was 20/200. The haze did not improve despite the use of topical corticosteroids; however, corneal clarity was restored, and vision improved with phototherapeutic keratectomy (PTK) and treatment with mitomycin-C (MMC) 0.02%. Late-onset stromal scarring can be triggered by systemic infection even years after PRK. PTK with MMC may be an effective treatment option for late-onset scars.

JCRS Online Case Rep 2021; 9:e00055 Copyright © 2021 Published by Wolters Kluwer on behalf of ASCRS and ESCRS

Over the past 30 years, photorefractive keratectomy (PRK) has been proven safe and effective for correcting low to moderate levels of refractive error. In most patients treated with PRK, before the introduction of mitomycin-C (MMC), surgery induced a mild transparent loss of the central cornea, commonly referred to as haze.1 The generation of corneal myofibroblast cells has been identified as the initial and principal biological cause of the formation of corneal haze. Factors previously associated with haze formation include major correction, depth of ablation, preoperative astigmatism, high or moderate myopia, hyperopia, high exposure to ultraviolet radiation, autoimmune conditions, the healing period of an epithelial defect, and irregularity of the postoperative stromal surface.2–5

Although uncommon, haze can also occur sporadically years or decades after PRK if the anterior cornea, especially the epithelial basement membrane, has been damaged (ultrastructurally or functionally).2 This allows a high amount of cytokines such as transforming growth factor-β to penetrate the corneal stroma and initiate myofibroblast differentiation.

A rare type of haze, termed late-onset haze (LOH), is typically more severe and carries a higher probability of vision loss.3,4 In the medical literature, some cases of LOH have been reported after viral conjunctivitis, chemical burns, trauma, autoimmune diseases, and ocular surgeries.4–7 Despite the several reasons known to trigger the development of an LOH, to our knowledge, this is the first time that chikungunya fever is attributed as the main cause.

Chikungunya virus (CHIKV) is an arbovirus transmitted to humans by the bite of infected mosquitoes.8 Given the wide distribution of its vector, it has a high potential to spread globally, including European countries and the United States.9 The typical clinical signs of the disease are abrupt onset of fever, headache, fatigue, and skin rash.8 Severe arthralgia with or without swelling is strongly predictive of chikungunya and may persist for months to years in some patients.8 Chikungunya can also cause ocular symptoms that may or may not be permanent.

We report a case of a late-onset scar that appeared more than 10 years after PRK, triggered by chikungunya infection, which was nonresponsive to corticosteroids. Phototherapeutic keratectomy (PTK) and MMC were indispensible in the improvement of vision.

Patient Consent Statement
Written consent was obtained from the patient to publish the details of the case.

CASE REPORT

A 42-year-old woman had PRK without MMC in 2007 for correction of 1.50 diopters (D) of myopia in both eyes with good visual outcomes. The postoperative central corneal thickness measured by 50 MHz ultrasonic pachymetry was 533.0 mm and 534.0 mm in the right and left eyes, respectively. In the interim, she presented with no complaints about her visual acuity, and although she had visited another clinic, the medical records were not available.
In May 2019, she was diagnosed with chikungunya fever through a positive immunoglobulin M antibody captured in enzyme-linked immunosorbent assay, and along with other systemic symptoms, she reported mild redness and photophobia of the left eye with no discharge. However, she was not seen by an ophthalmologist at that time.

Two weeks after the infection, she noticed acute impairment of visual acuity in the left eye, hence returned to our facility. On initial examination, her visual acuity was 20/20 in the right eye and 20/200 in the left eye. There was no improvement noted on correction or with rigid contact lens. The right eye was normal; however, the left eye had a dense superficial stromal scar over the pupil, measuring 6.0 mm at its greatest diameter (Figures 1 and 2). The surface of the scar was grossly irregular, and the central corneal thickness on the high-resolution rotating Scheimpflug device (Pentacam HR—Oculus) and on anterior segment optical coherence tomography (OCT) (Cirrus HD-OCT 5000/500) was 661 µm and 690 µm in the left eye and 539 µm and 544 µm in the right eye, respectively. No conjunctival injection was observed, and the remaining anterior segment structures were normal. The dilated fundus examination performed was unremarkable. The patient was prescribed topical prednisolone acetate 1.0% 4 times a day for a month. However, no improvement in vision or corneal appearance was observed.

Three months after the diagnosis, because of the patient’s complaints, severity of visual disability, and the intensity of corneal opacity, manual debridement combined with phototherapeutic keratectomy of the left eye was performed. MMC 0.02% was applied for 1 minute after the ablation, and the total amount of the ablated cornea was approximately 100 µm. One week after the surgery, the patient reported mild improvement in her vision. At 1 month, her corrected distance visual acuity was 20/80, and the haze seemed to have comparatively diminished (Figures 3 to 5).

Nine months after the surgery, her visual acuity remained stable, and rigid gas-permeable contact lens fitting was tried again. This time, smoother surface and more transparency was noted than before, and thus, she achieved a visual acuity of 20/25 on the left eye with mild apical clearance, centration, and good movement; she refused additional surgeries.

**DISCUSSION**

Haze is corneal transparency loss resulting from changes in the corneal cell density and phenotype after refractive surgery. Refractive surgery leads to the production of disorganized extracellular matrix components.\(^1\) The incidence rates of LOH after PRK can be estimated as 1% to 4% depending on the class and degree of ametropia and the use of MMC and its application time.\(^2\) In our case, the surgery was performed without MMC prophylaxis. However, LOH may occur despite the use of this potent mitotic inhibitor.

---

**Figure 1.** Slitlamp image on diffuse illumination of the anterior biomicroscopy of a patient with central corneal opacity during chikungunya infection in the left eye. A severe loss of corneal clarity due to nonuniform scar tissue present on the anterior stroma and epithelium.

**Figure 2.** Same patient, diffuse illumination, 1 month after phototherapeutic keratectomy with mitomycin-C showing improvement of surface smoothness and corneal transparency.

**Figure 3.** Same patient on retroillumination disclosed a grossly irregular corneal surface and cloudiness: *Left*, before PTK; *Right*, 8 months after PTK. PTK = phototherapeutic keratectomy
Teus et al. reported a case of LOH resulting from epithelial trauma 1 year after laser-assisted subepithelial keratectomy even with the use of intraoperative MMC0.02%. Other authors have reported similar cases, which may indicate that MMC treatment may not be effective in preventing LOH. Kuo et al. reported a 1.8% incidence of LOH associated with myopic regression in a cohort of 542 patients, and they found a positive correlation between LOH and the amount of attempted correction. Cua and Pepose reported a case of unilateral LOH 1 year after the retreatment of PRK in a patient with a recent diagnosis of systemic lupus erythematosus. They support the concept that patients with autoimmune disorders may be at higher risk for developing corneal scars after PRK.

A widely believed opinion and one of the most intriguing aspects of haze formation is that it is rarely seen in eyes with lower levels of myopia corrected with PRK. However, in our case, the patient underwent PRK to correct only 1.50 D of spherical myopia with no astigmatism associated. Although the occurrence of vision-disturbing central opacity is unusual after PRK for low myopia, the case described in this study illustrates the potential for severe central corneal scarring in patients with a systemic viral infection, specifically an arbovirus infection. Similar cases have been reported as secondary to ocular viral infections.

The clinical appearance and OCT findings of our case may resemble Salzmann degeneration to some cornea specialists. In fact, these 2 entities share certain histopathological features, have similar etiologies, and the OCT and ultrasound biomicroscopy images may be comparable. We diagnosed this case as LOH owing to the acute onset of the lesions and the history of PRK surgery (Table 1).

Chikungunya is an arbovirus, such as the dengue and Zika virus. This RNA virus is a member of the Alphavirus genus from the Togaviridae family, which is transmitted to humans by the bite of infected mosquitoes, usually from the genus Aedes. The spread of these vectors preceded the global expansion of the arboviruses, and recent massive outbreaks were seen in different countries. CHIKV is an arbovirus with likelihood to spread globally.

Ocular manifestations of chikungunya fever are not common but can include keratitis, episcleritis, uveitis, optic neuritis, and retinitis, and these ocular manifestations can be present at the time of systemic illness or after the resolution of the systemic disease. During the initial phase of the disease, patients could present with photophobia, retroocular pain, and conjunctivitis that is self-limited resembling other viral infections. Based on the literature, the involvement of the corneal surface could include punctate superficial keratitis, stromal keratouveitis, keratic precipitates with a dendritic pattern, and corneal edema. CHIKV has already been detected by real-time polymerase chain reaction in the aqueous humor of patients with ocular symptoms associated with systemic infection. Hayek et al. reported a case of bilateral stromal keratouveitis in a patient with a history of CHIKV infection, who had positive real-time polymerase chain reaction results in aqueous humor. These findings suggest that the virus may...
spread from the blood or the central nervous system to the ocular tissues, potentially damaging the vision.

Notably, CHIKV was identified in the corneal grafts of patients with positive serology for chikungunya, even when they were asymptomatic, and these ocular tissues may represent an actual risk for viral transmission. The long-lasting effects of chikungunya fever, especially those related to arthralgia, are more common in sites already damaged by underlying disorders, such as osteoarthritis. We postulate that this corneal scar would not have occurred if the patient had not undergone corneal surgery. It is possible that the absence of Bowman layer makes the cornea more susceptible to reactive scarring from subsequent minor injuries.

Some authors hypothesize that the mechanism behind haze formation is the myofibroblast generation from progenitor cells, modulated by the influx of cytokines from the epithelium into the stroma through a defective basement membrane. Furthermore, it is already known that CHIKV targets fibroblasts from the deep dermis and fibroblasts from the eye, including those of the corneal and scleral stroma and the corneal endothelium. Thus, the primary cause of haze in this case could be the direct action of the virus; however, we are unable to confirm this hypothesis.

Despite the hypotheses from previous reports, the mechanism by which the CHIKV affects the eye, more specifically the cornea, is not elucidated yet; it could be by direct action of the virus or an immune-based inflammation. Hence, we cannot ascertain that the haze of this patient is secondary to the virus or an immune-mediated reaction secondary to a systemic infection. However, it is possible that these 2 different mechanisms are synergistically involved in triggering the scar formation in this case.

The late-onset scar of our patient was not related to the PRK surgery itself. She had a low degree of myopia, and the procedure was unremarkable and had a small ablation depth. Furthermore, she had a regular and fast epithelial recovery and remained absolutely normal for more than 12 years. No attributing risk factors pointed out by other authors were observed in this case.

This case report has several limitations. First, the patient was not seen during the onset of the red eye. In addition, complementary serologic tests to rule out other diseases such as tuberculosis, cytomegalovirus, or hepatitis were not performed. Moreover, spontaneous resolution of the opacity over time was not considered. In addition, the finding of a corneal haze in a nondominant eye may raise the question of whether this opacity really appeared concurrently with the viral infection. However, as the patient stated, she visited an ophthalmologist regularly in her city, and she always passed the driver’s license visual acuity examination easily. Hence, we can consider the possibility that she did not have any major disease in her left eye.

Despite these questions, the corneal haze appeared at the same time as the chikungunya infection was confirmed by enzyme-linked immunosorbent assay. The clinical intensity of the lesion was very severe. To the authors’ knowledge, this is the first description of a presumed LOH after PRK in a patient who had chikungunya infection.

### Table 1. Comparison Between Late-Onset PRK-Related Haze and Salzmann Nodular Degeneration.

| Points to observe | Late-onset haze after PRK | Salzmann degeneration |
|-------------------|---------------------------|-----------------------|
| Clinical aspects  | Diffuse opacity of the anterior stroma. May be irregular or smooth. | Yellowish-white to blue elevated subepithelial nodules usually arranged in a circular fashion and in the midperiphery. |
| Onset             | May be acute after a trigger. | Usually develop slowly and gradually. |
| Risk factors      | Large treatments and ablation depth, autoimmune conditions, high UV radiation, trauma, and others. | Chronic ocular surface irritation. |
| Possible mechanism| Myofibroblast generation from progenitor cells, modulated by the influx of cytokines from the epithelium into the stroma through a defective basement membrane. | Interruption of epithelial basement membrane allows cell debris and cytoplasmic fibrillar material to be released into the stroma. |
| Histopathology    | Epithelial hyperplasia, a sharply defined excision of Bowman layer in the periphery of the ablation site, the presence of newly formed type III disorganized collagen, vacuolation of keratocytes and their activation to fibrocytes, and the existence of proteoglycan matrix. | Dense basement membrane–like material overlying stromal disorganization, obliterating Bowman layer and covered by a thinned layer of epithelium. Presence of newly formed type III disorganized collagen. |
| OCT               | Hyperreflectivity in the subepithelial layer and anterior stroma. | Absence of the Bowman layer that is partially replaced by a granular PAS-positive material. |

**PRK** = photorefractive keratectomy

**WHAT WAS KNOWN**

- Haze after photorefractive keratectomy may occur years postoperatively, resulting in considerable visual impairment.
- Several causes, such as viral conjunctivitis, chemical burns, trauma, and ocular surgeries, have been listed as possible triggers of late-onset haze.

**WHAT THIS PAPER ADDS**

- Systemic viral infections, such as chikungunya fever, might also trigger this rare condition.
- As these viral systemic diseases have become more common in recent years, ophthalmologists must be aware that they may affect the eye in different and unexpected ways, including corneal scars in patients treated with photorefractive keratectomy, even years after the surgery.
REFERENCES
1. Marshall J, Trokel SL, Rothery S, Krueger RR. Long-term healing of the central cornea after photorefractive keratectomy using an excimer laser. Ophthalmology 1988;95:1411–1421
2. Netto MV, Mohan RR, Sinha S, Sharma A, Dupps W, Wilson SE. Stromal haze, myofibroblasts, and surface irregularity after PRK. Exp Eye Res 2006;82:788–797
3. Stojanovic A, Nitter TA. Correlation between ultraviolet radiation level and the incidence of late-onset corneal haze after photorefractive keratectomy. J Cataract Refract Surg 2001;27:404–410
4. Gomes BA, Smadja D, Espana EM, Ahn ES, Netto MV, Santhiago MR. Very late-onset corneal scar triggered by trauma after photorefractive keratectomy. J Cataract Refract Surg 2012;38:1694–1697
5. Cua IY, Pepose JS. Late corneal scarring after photorefractive keratectomy concurrent with development of systemic lupus erythematosus. J Refract Surg 2002;18:750–752
6. Campos M, Takahashi R, Tanaka H, Chamon W, Allemann N. Inflammation-related scarring after photorefractive keratectomy. Cornea 1998;17:607–610
7. Teus MA, de Benito-Ulips LD, Alió JL. Mitomycin C in corneal refractive surgery. Surv Ophthalmol 2009;54:487–502
8. Couderc T, Lecuit M. Chikungunya virus pathogenesis: from bedside to bench. Antivir Res 2015;121:120–131
9. de Andrade GC, Ventura CV, Mello Filho PA, Maia M, Vianello S, Rodrigues EB. Arboviruses and the eye. Int J Retina Vitreous 2017;3:4
10. Kuo IC, Lee SM, Hwang DG. Late-onset corneal haze and myopic re- gression after photorefractive kerectomy (PRK). Cornea 2004;23:350–355
11. Wood TO. Salzmann’s nodular degeneration. Cornea 1990;9:17–22
12. Das S, Link B, Seitz B. Salzmann’s nodular degeneration of the cornea. Cornea 2005;24:772–777
13. Lalitha P, Rathinas S, Banushree K, Maheshkumar S, Vijayakumar R, Sathe P. Ocular involvement associated with an epidemic outbreak of Chikungunya virus infection. Am J Ophthalmol 2007;144:552–556
14. Hayek S, Rousseau A, Bouthry E, Pratt CM, Labetoulle M. Chikungunya virus infection and bilateral stromal keratouveitis. JAMA Ophthalmol 2015;133:849–850
15. Couderc T, Gangneux N, Chrétien F, Caro V, Le Luong T, Ducloix B, Tolou H, Lecuit M, Grandadam M. Chikungunya virus infection of corneal grafts. J Infect Dis 2012;206:851–859

Disclosures: None reported.

First author:
Renato Correa Souza de Oliveira, MD
Instituto Brasileiro de Oftalmologia, Praia de Botafogo, Rio de Janeiro, Brazil