American Journal of Ophthalmology Case Reports 25 (2022) 101243

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Case report

Atypical presentation of acanthamoeba keratitis resembling central toxic keratopathy

Mathew S. Ward [a], Jordan P. Hastings [b], Kathryn M. Shmunes [a], Yasmyne Ronquillo [a], Phillip C. Hoopes [a], Majid Moshirfar [c,d,e,*]

[a] Riverwoods Eye Center, Provo, UT, USA
[b] California Northstate University College of Medicine, Elk Grove, CA, USA
[c] Hoopes Vision Research Center, Draper, UT, USA
[d] John A. Moran Eye Center, University of Utah School of Medicine, Salt Lake City, UT, USA
[e] Utah Lions Eye Bank, Murray, UT, USA

ARTICLE INFO

Keywords:
Acanthamoeba
Keratitis
Central toxic keratopathy
CTK

ABSTRACT

Purpose: To describe an atypical case of acanthamoeba keratitis with positive in vivo confocal microscopy in a non-contact lens user who presented with signs and symptoms suggestive of central toxic keratopathy.

Observations: The patient presented with bilateral, though sequential, decreased visual acuity with mild pain. Examination showed stromal haze with corneal flattening and thinning without epithelial defects. Optical coherence tonometry of the right eye revealed an inverse dome-shaped appearance of the opacity and in-vivo confocal imaging showed double-walled cysts consistent with acanthamoeba. Corneal haze, stromal loss, resolved and visual acuity improved over time.

Conclusion and importance: Acanthamoeba is a rare cause of infectious keratitis that is most often associated with contact lens wear in developed countries. Typically, it presents with a unilateral decrease in visual acuity, photophobia, watering, and pain that is out of proportion to slit lamp examination findings. However, many atypical presentations have been reported in the literature. Consequently, it may be misdiagnosed, especially early in the course of the disease. This delay in diagnosis can lead to progressive ulceration and visual impairment. In addition, cyst formation can make eradication with anti-amoebic treatment especially difficult.

Central toxic keratopathy is a non-inflammatory clinical syndrome of unknown etiology that is most often associated with excimer laser ablation, though other associated causes have been reported. It is characterized by a central or paracentral opacity with corneal stromal loss and resultant hyperopic shift. The opacification and stromal loss mostly resolve over the course of months with an improvement in visual acuity. This report may help physicians broaden their differential and correctly diagnose atypical presentations of amoebic infection.

1. Introduction

Acanthamoeba is a rare, vision-threatening cause of microbial keratitis with potentially devastating outcomes.[1–5] The genus *acanthamoeba* consists of more than 20 species, at least eight of which have been reported to cause keratitis in humans. Acanthamoeba are ubiquitous protozoa that have been isolated from air, soil, dust, water, and even the nasopharyngeal mucosa of unaffected healthy individuals.[6,7] While idiopathic infections do occur, in developed countries, the disease is most commonly reported in contact lens wearers,[4,5] though cases have been reported in non-contact lens wearers. Non-contact lens use keratitis may be more common in developing countries.[4,8] To our knowledge, all cases of bilateral acanthamoeba keratitis have been associated with contact lens use.[1,9–17] Diagnosis is difficult clinically, as a wide array of corneal manifestations are possible.[3–5] This case describes a patient without a history of contact lens wear who had an atypical presentation of acanthamoeba keratitis, but with slit lamp examination findings suggestive of central toxic keratopathy (CTK).

Acanthamoeba can have varying presentations, but classically presents in a contact lens user with unilateral tearing, photophobia, pain out of proportion to exam, and a decrease in visual acuity.[1–5] Progression of the infection can lead to a white stromal ring infiltrate, radial

* Corresponding author. HDR Research Center, Hoopes Vision, Draper, UT, USA.
E-mail address: Cornea2020@me.com (M. Moshirfar).

https://doi.org/10.1016/j.ajoc.2021.101243
Received 13 October 2020; Received in revised form 25 August 2021; Accepted 13 December 2021
Available online 16 December 2021

keratoneuritis, corneal ulceration, and anterior uveitis with or without hypopyon.[3–5,18,19] In the early stages of the disease, the clinical findings in acanthamoeba keratitis are non-specific, and lead to misdiagnosis. It has been reported that cases of early acanthamoeba infections are misattributed to herpetic keratitis 47.6% of the time, or, less commonly, mycotic (25.2%) or bacterial keratitis (3.9%).[4,5,20]

Atypical cases may also present with more indolent symptoms, including presentations without pain,[21,22] radial keratoneuritis,[4] epithelial defects,[21] or contact lens wear.[8] The duration and the process of acquiring infection, can cause variable corneal manifestations ranging from punctate epithelial erosions to multifocal stromal infiltrates, nummular keratitis (with or without stromal edema and keratic precipitates), and even dendriform patterns.[4,5,23] Additionally, viral, fungal, and bacterial keratitis have also been documented to coexist with cases of acanthamoeba and can delay diagnosis.[24–27] Damage from herpesvirus specifically has been hypothesized to affect the corneal epithelium in such a way that predisposes to acanthamoeba keratitis.[27]

CTK is a newly recognized clinical syndrome with a yet unknown non-inflammatory cause. This rare pathology is characterized by central corneal opacification, stromal loss, and hyperopic shift, usually within seven days of photorefractive surgery (e.g., laser assisted keratomileusis (LASIK) or photorefractive keratopathy (PRK)).[28,29] Blurry vision, photophobia, pain, halos, and a foreign body sensation may be present.[29] Cases without excimer laser ablation have also been reported in contact lens wearers and idiopathically.[30–33] After its formation, the opacity persists for 2–18 months before resolving. Though most affected corneas clear significantly within one year, stromal thinning and residual decrease in visual acuity may persist.[28,29] Optical coherence

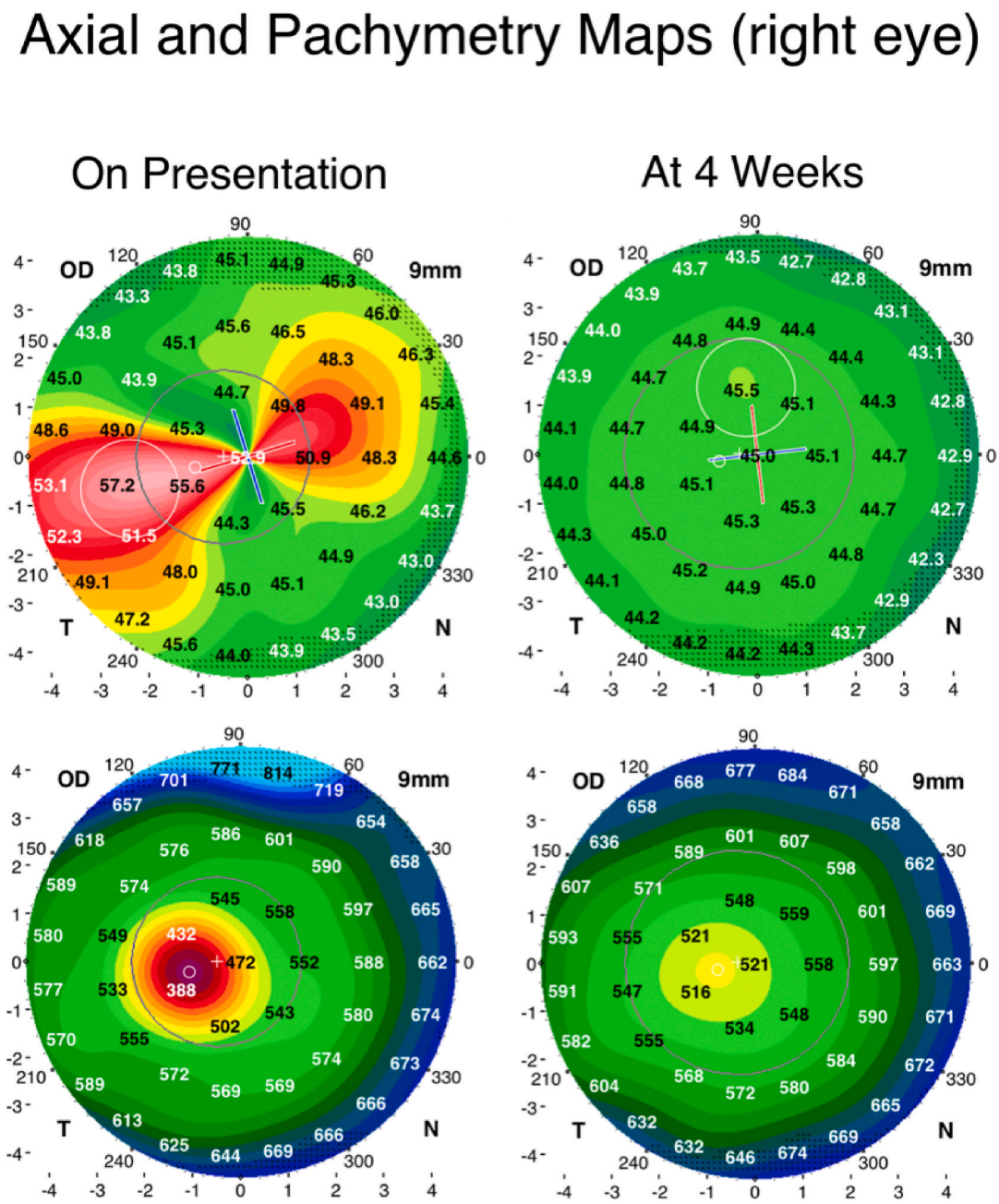

Fig. 1. Right eye examination with Ziemer Galilei G2 Dual Scheimpflug Analyzer. Initial presentation shows acute temporal paracentral corneal thinning in the area associated with the opacity. Architectural changes resulted in induced astigmatism. At one month, there is a return to baseline corneal curvature and resolution of his astigmatism.

tomography (OCT) (Optovue Inc, Irvine, Ca) imaging may reveal thinning of the corneal stroma with an inverse dome-shaped opacity that extends through the width of the stroma.[28,30] The recommended treatment is supportive with close follow up, as the opacity clears to a degree with time, and invasive interventions have not proven to be superior.[29]

The aim of this report is to present a unique case of atypical presentation of acanthamoeba keratitis which presented with signs and symptoms of central toxic keratopathy. and has not been reported in the literature. This report gives an insight into the pathophysiology of both diseases.

2. Case presentation

The patient is a 15-year-old male who was referred to the clinic with blurry vision in his right eye (OD) and mild pain of five days duration with no changes in his left eye (OS). Ocular and medical history were unremarkable, and the patient did not wear contact lenses. He denied previous episodes of bacterial or viral keratitis, and there was no reported trauma or known exposure to potentially contaminated water or soil. Best corrected visual acuity was 20/40 OD and 20/15 OS.

On examination, the anterior chamber, iris, lens, vitreous, and fundus exam were unremarkable in both eyes (OU). However, there was a temporal paracentral corneal opacity measuring 1.5 × 1.5 mm with some surrounding mid-stromal haze OD. Keratic precipitates and pseudoguttata were not noted in this opacified area. In the area of the opacity there was corneal flattening without epithelial defects which led to induced irregular astigmatism. His right eye was 360 μm at its thinnest point with K values of 44.28 @ 107°/54.75 @ 17°. This led to 10.47 diopters of astigmatism (Fig. 1). His left eye was unremarkable on examination, and topographic imaging demonstrated K values of 45.14 @ 156°/45.91 @ 66° with a thickness of 529 μm (Fig. 2).

While the diagnosis was uncertain, the patient was empirically treated with oral acyclovir 400mg five times daily, and topical prednisolone one drop five times a day for presumed disciform herpes simplex virus (HSV), a microbe known to have atypical presentations. Within one week, the patient's vision was 20/25 OD, with residual complaints of mild blurry vision. Subsequently, his medications were tapered and discontinued. The central opacity largely resolved within four weeks of initial presentation with best corrected visual acuity 20/15 in both eyes. Topography showed a return to the baseline corneal curvature with right eye K values of 44.97 @ 97°/45.38 @ 7° allowing his astigmatism to resolve to 0.41 diopters (Fig. 2).

Approximately eight months after the initial visit, the patient had a recurrent episode with a similar appearance. He presented with blurry vision, mild pain, and light sensitivity in his right eye for one day. Visual acuity was 20/30 OD, and a diffuse haze without epithelial defects or focal infiltrates was again noted in the cornea. He was treated with topical Tobramycin - Dexamethasone (Tobradex) three times a day and oral valacyclovir 1000mg twice a day for ten days. He again improved within one month.

Two months following the recurrence of corneal haze in his right eye, he presented again for a one-week duration of painless blurry vision, photophobia, and redness in his left eye. Previously, his left eye had been symptom-free and showed no irregularities on topographic imaging or examination with K values of 45.14 @ 156°/45.91 @ 66° and the thinnest portion measuring 529 μm thick (Fig. 2). He reported no pain. Visual acuity was 20/60 OS. A central amorphous circular paracentral corneal mid-stromal opacity (2 × 2 mm) without an overlying epithelial defect was noted to be present (Fig. 3). Slit lamp examination showed unremarkable conjunctiva, sclera, anterior chamber, iris, lens, and vitreous OU, and no corneal opacities in the right eye.

Empiric treatment with antivirals and steroids for presumed herpetic disciform keratitis was initiated. However, the patient did not respond to treatment. There was no change at one week follow up, and the patient

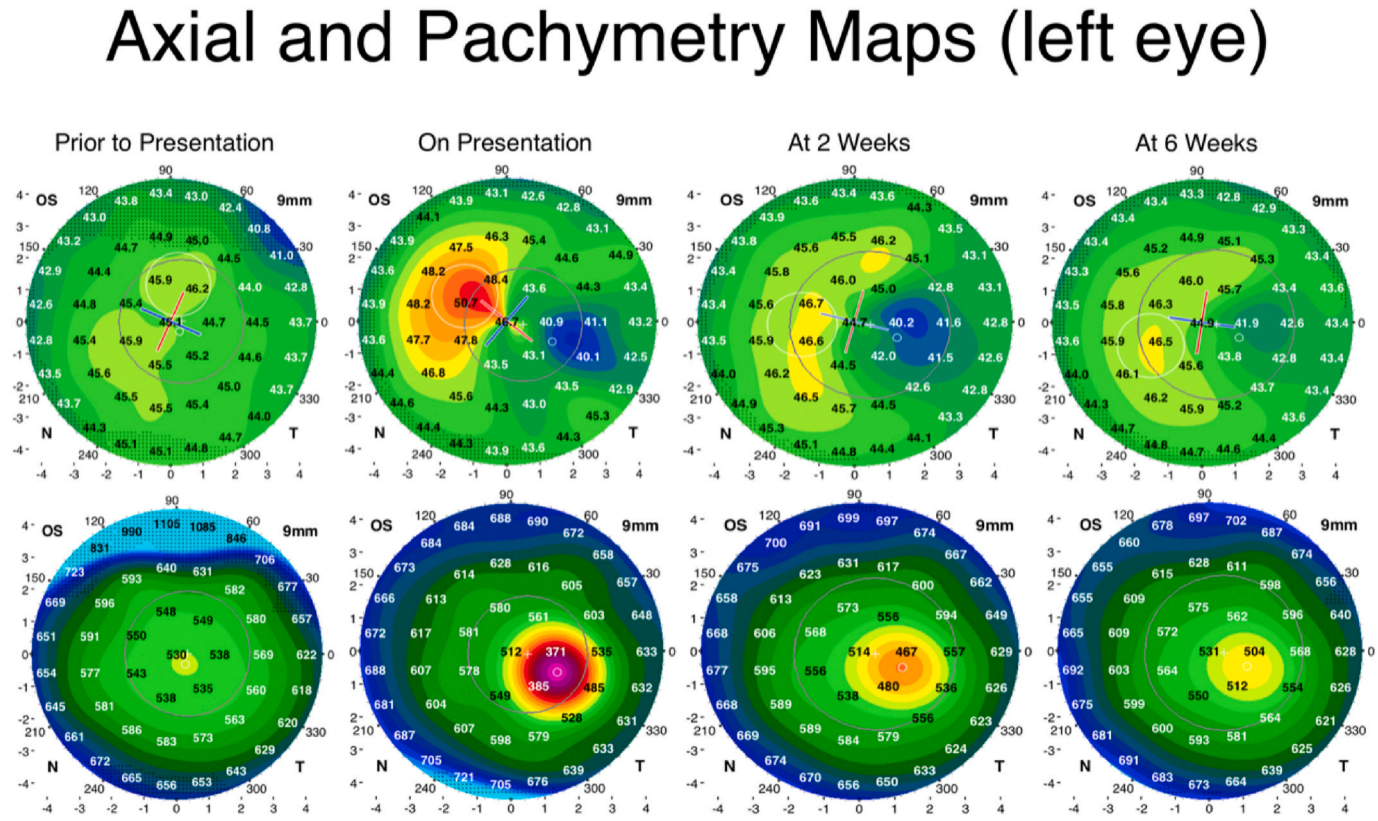

Fig. 2. Left eye examination with Ziemer Galilei G2 Dual Scheimpflug Analyzer. Normal findings prior to initial presentation. Initial presentation showing normal findings. A paracentral and temporal area of corneal thinning was noted in the area of the opacification. This reduced stromal volume led to induced astigmatism. The cornea gradually returned to normal at 6 weeks. Corneal thickness has increased in thickness.

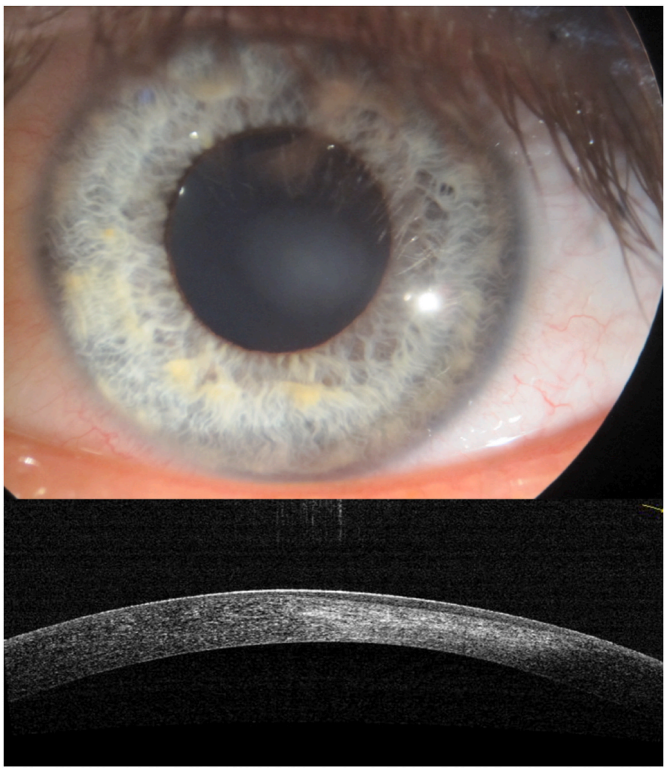

Fig. 3. Slit lamp photograph of the left eye on initial presentation. This occurred two months after resolution of the prior lesion in the patient's right eye, which had a similar appearance. The corresponding OCT shows inverse dome-shaped opacity spanning the anterior and posterior stroma. Thinning is observable in the inferior aspect of the cornea over the area of opacification.

continued to have painless blurry vision. Slit lamp examination again showed a central 2 × 2 mm mid-stromal haze that was unchanged in size, and mild decrease in the density. Stippling was observed just anterior to the area of haze. At this point, anterior segment OCT imaging showed a central opacity with an inverse dome-shaped appearance within the stroma. An area of corneal flattening with decreased thickness (440 μm reduced from baseline 529 μm [Fig. 2]) was observed in the left eye (Fig. 3). Topographic imaging revealed an area of temporal paracentral flattening when compared to his baseline ten months prior. K values of 44.21 @ 51°/46.99 @ 141° led to induced astigmatism of 2.77 diopters (Fig. 2). Confocal imaging (ConfoScan4, Nidek, Japan) was obtained and was positive for double-walled cysts consistent with acanthamoeba keratitis, the circle hyperintensity identifies a cyst (Fig. 4).

Chlorhexidine 0.02% (compounded at the Moran Eye Center) and propamidine isethionate 1 mg/ml (Sanofi-Aventis Pharma, United Kingdom) one drop hourly while awake were added to oral valacyclovir 1000mg twice daily and topical prednisolone one drop twice daily. Five days later, the visual acuity had improved to 20/50, and the haze appeared less dense. On additional follow up nine days later (two weeks after the initiation of anti-amoebic therapy), epithelial scraping samples were obtained for polymerase chain reaction (PCR) testing, which eventually returned negative. Gradual improvement was noted, and two weeks later visual acuity improved to 20/30 in his left eye.

Similar to the clinical course of the previously affected right eye, topographic imaging revealed a progressive return to the baseline corneal curvature in the area of previous flattening, and astigmatism reduced to 1.29 diopters (Fig. 1). Chlorhexidine and propamidine isethionate were reduced to four times daily for one week and stopped; prednisolone was tapered and stopped. Approximately nine weeks after presentation, the cornea was clear without visible haze. Best corrected visual acuity was 20/20 OD and 20/25 OS. Tomography showed

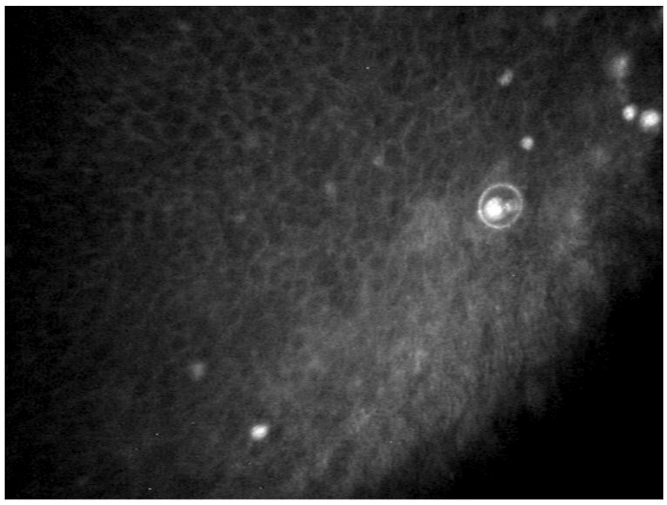

Fig. 4. Confocal microscopy imaging of the left eye showing double-walled cysts, consistent with acanthamoeba.

residual corneal changes with K values 44.39 @ 166°/45.64 @ 76° and irregular astigmatism of 1.25 diopters, much improved from prior K values of 44.21 @ 51°/46.99 @ 141° with 2.77 diopters of astigmatism. There was no residual scarring or haze. The cornea had thickened 47 μm to 487 μm (from 440 μm) at the thinnest point (Fig. 3).

3. Discussion

In summary, our patient is a 15-year-old male with no contact lens use who presented with two episodes of decreased visual acuity in the right eye that was associated with mild pain. Examination revealed a central opacity and corneal thinning in the affected eye that returned to baseline within one week with antiviral treatment for presumed disciform herpetic keratitis. Two months following his second episode in the right eye he had a similar presentation in his left eye. However, there was no response to antiviral treatment. Additional workup revealed double-walled cysts on confocal microscopy, consistent with acanthamoeba keratitis. With anti-amoebic treatment, the stromal loss and haze resolved and the visual acuity improved.

Due to the atypical presentation and nonspecific findings, the differential diagnosis in our case was extensive. Initially, the patient was believed to have disciform herpetic keratitis as HSV can present with corneal topographic irregularity and opacity. These lesions are generally unilateral (0.8% reportedly bilateral) and inflammatory in nature. They often affect the corneal epithelium or endothelium and may be recurrent in nature. Endotheliitis has been reported as a key presenting sign in 4 patients who were soft contact lens wearers.[34] Disciform lesions may often present with keratic precipitates, pseudoguttata, trabecular inflammation, elevated intraocular pressures, and dilated iris vasculature.[35,36] Keratoneuritis without any associated epithelial defect or pain was reported in a 15 year-old contact lens wearer who had complaints of redness and discomfort.[21] Though acanthamoeba causes a chronic keratitis, the first case of fulminant acanthamoeba endophthalmitis with scleritis after cataract surgery has been reported.[37]

Our patient had bilateral (though sequential) disease with no prior history of herpetic keratitis in either eye or dendritic lesions, no keratic precipitates or pseudoguttata, no inflammation noted on examination, and a rapid recovery time. These findings made HSV keratitis unlikely.[35,36] Bacterial keratitis was considered, but a lack of discharge, trauma, contact lens use, anterior chamber reaction, conjunctival injection, or pain made this less likely.[38] A rare and unusual dendrite-like anterior stromal keratitis has been reported from coinfection with Acanthamoeba and *Pseudomonas aeruginosa* in a contact lens wearer.[39]

Other organisms known to cause keratitis were also considered such,

as fungi, but a lack of characteristic signs (epithelial defect, satellite lesions, anterior chamber reaction, feathery borders, purulent secretions, or an immunocompromised state) also made this diagnosis less likely.[40] Due to the recurrent, bilateral nature of his disease and associated opacification, keratoendotheliitis fugax hereditaria should also be considered, but his lack of family history, Finnish heritage, pain, and general rarity made this unlikely as well. Confocal microscopy showing the double-walled cyst and round hyperreflective spots characteristic of acanthamoeba keratitis positively identified the causative pathogen.[41] In the context of strongly positive confocal imaging, and the evidence against other diagnoses, a final diagnosis of amoebic keratitis with an atypical presentation was made as the only possible explanation for his unique case.

Our patient had an atypical case of acanthamoeba, which presented similar to CTK. The central stromal amorphous opacity, corneal thinning and flattening, photophobia, and decreased visual acuity are all features associated with CTK. Additionally, OCT imaging revealed the opacity had an inverse dome-shape appearance.[28–30] In addition to these findings, the lack of pain or epithelial defect is an unusual presentation for acanthamoeba keratitis. Finally, the patient had no risk factors for acanthamoeba keratitis or CTK, making the case more interesting, and diagnosis more difficult.

Antibodies against acanthamoeba have been isolated in the human nose and throat of healthy individuals without prior known infection.[42,43] Additionally, acanthamoeba species have been cultured in up to 10% of contact lens storage cases, although acanthamoeba keratitis is estimated at less than 2.01 cases per million contact lens users.[6] This may indicate that there may be subclinical or self-limiting infections of this parasite. However, it should be noted that serum immunoglobulins may not be efficacious at limiting corneal infection.[6]

Classically, we ascribe acanthamoeba to be a disease that is difficult to eradicate and indicates a poor prognosis; however, this teaching may not be entirely correct. We hypothesize that some cases of acanthamoeba may resolve, and thus, no medical care would be sought by the patient. Some cases may have been treated with non-anti-parasitic agents and the disease resolved due to the body's natural innate immune system. With the increase of atypical cases of acanthamoeba in recent years it is also possible that a yet uncharacterized species, or perhaps a known species that was previously thought to be nonvirulent, is causing unique presentations. Our case indicates a possible moderate successive bilateral acanthamoeba infection without contact lens use that presented with signs resembling CTK. Whereas one eye was infected and self-resolved with coinciding antiviral treatment, a more virulent strain in the other eye necessitated, and responded to, pharmacotherapy for resolution. The nature of the pathology in the right eye is more speculative as confocal microscopy was not performed.

There are limitations to our case report, most prominently a negative PCR result. However, it should be noted that various PCR assays for acanthamoeba have shown to return false negatives for both typical and atypical strains.[44] The analyzed sample was collected fourteen days after the initiation of antiparasitic treatment, which may have affected the results. Additionally, the patient's epithelium, which was sent for analysis, was intact, and the opacity and cyst on confocal imaging were found in the deeper stroma, likely making the PCR sample a less sensitive test.

In vivo confocal microscopy has high sensitivity and specificity for acanthamoeba, even in cases with negative corneal scraping or atypical presentations.[21,45] Two reports have described the efficacy of this test in the diagnosis of acanthamoeba keratitis. Sensitivity has been reported at 88.9%–100% and 90.6%–92.9% with specificities reported at 100% and 77.3%–100%.[41,45] Conversely, the same studies reported that the sensitivity of PCR in the diagnosis of acanthamoeba is 66.7%–75%, and specificity is 100%.[41] A positive test result in either of these tests is highly predictive, since the positive predictive value has been reported at 100% for both. Conversely, a negative test result is not as helpful since the negative predictive values for PCR are 75%[41] when using the loosest definitions for diagnosis (defined as 'definite acanthamoeba keratitis').[45]

We believe that the confocal imaging and response to amoeba treatment in the left eye confirms the diagnosis. This falls under Tu et al.'s 'definite acanthamoeba keratitis' classification of a positive acanthamoeba infection, and is represented by the sensitivity and specificity values previously stated.[45] However, another cyst forming pathogen (e.g., cryptosporidium) could be a potential cause.[46,47]

Another limitation to our report is that we did not obtain confocal microscopy evidence in his initial right eye presentation one year ago, and it is not definite that it was also a case of acanthamoeba keratitis. Moreover, the previous lesion's resolution with concomitant antiviral treatment makes an alternative explanation, such as disciform herpetic keratitis possible, even in the absence of characteristic features of that disease.

The etiology of CTK is not established, though many theories have been proposed, including complications due to various aspects of surgical care,[28,29,48,49] meibomian gland secretions,[29] antigen-antibody complexes,[50] as well as inflammatory cytokines and metalloproteases.[30] Our case, which presented very similarly to classic descriptions of CTK, may provide additional information to the underlying incompletely understood pathology. Additionally, it is a unique case of amoebic infection in a non-contact lens user, which may help clinicians widen their differential in cases of keratitis to include atypical presentations of amoebic infections. We hope that this allows for a better understanding and faster diagnosis of amoebic keratitis.

4. Conclusion

We present a unique case of atypical presentation of acanthamoeba keratitis which presented with signs and symptoms suggestive of central toxic keratopathy. This case report provides an additional atypical presentation to help broaden the differential diagnosis in patients with similarly presenting corneal lesions. Additionally, the similarity to central toxic keratopathy may provide clues to the etiology of this clinical syndrome.

Publication originality statement

We confirm this publication is original.

Location

Patient was examined and treated at the Riverwoods Eye Center in Provo, Utah.

All figures and photos

Dr. Matthew Ward files.

Patient consent/research ethics

The patient and Father have provided written consent for the publication of this case report. The Hoopes Vision Ethics Board approved this publication.

Funding

This study was funded by an unrestricted grant from Research to Prevent Blindness (RPB), 360 Lexington Avenue, 22nd Floor New York, NY 10017. No support was received for the publication of this article.

Authors

All authors attest that they meet the current ICMJE criteria for Authorship. Additionally, they take responsibility for the integrity of the

work, and have given final approval to the version to be published.

Declaration of competing interest

None of the authors have any conflict of interest related to this work. The following authors have no financial disclosures: MW, JH, KS, YR, PH, MM.

Acknowledgement

None.

References

1. Wilhelmus KR, Jones DB, Matoba AY, Hamill MB, Pflugfelder SC, Weikert MP. Bilateral acanthamoeba keratitis. *Am J Ophthalmol*. 2008;145(2). https://doi.org/10.1016/j.ajo.2007.09.037.
2. Khan YA, Kashiwabuchi RT, Martins SA, et al. Riboflavin and ultraviolet light a therapy as an adjuvant treatment for medically refractive acanthamoeba keratitis: report of 3 cases. *Ophthalmology*. 2011;118(2):324–331. https://doi.org/10.1016/j.ophtha.2010.06.041.
3. Putri Dian Eka, Edwar Lukman, Susiyanti M. Acanthamoeba keratitis in a non-contact lens wearer: a challenge in diagnosis and management. *J Case Rep*. 2014;4:419–423.
4. Garg P, Kalra P, Joseph J. Non-contact lens related Acanthamoeba keratitis. *Indian J Ophthalmol*. 2017;65(11):1079. https://doi.org/10.4103/ijo.IJO_826_17.
5. Szentmáry N, Daas L, Shi L, et al. Acanthamoeba keratitis – clinical signs, differential diagnosis and treatment. *J Curr Ophthalmol*. 2019. https://doi.org/10.1016/j.joco.2018.09.008.
6. Niederkorn JY, Alizadeh H, Leher H, McCulley JP. The pathogenesis of Acanthamoeba keratitis. *Microb Infect*. 1999. https://doi.org/10.1016/S1286-4579(99)80047-1.
7. Clarke DW, Niederkorn JY. The pathophysiology of Acanthamoeba keratitis. *Trends Parasitol*. 2006;22(4):175–180. https://doi.org/10.1016/j.pt.2006.02.004.
8. Erdem E, Evcil Y, Yagmur M, Eroglu F, Koltas S, Ersoz R. Non-contact lens use-related acanthamoeba keratitis in Southern Turkey: evaluation of risk factors and clinical features. *Eur J Ophthalmol*. 2013. https://doi.org/10.5301/ejo.5000357.
9. Holz FG, Burk ROW, Volcker HE. BILATERALE AKANTHAMOBEN-keratitis. *Klin Monbl Augenheilkd*. 1993. https://doi.org/10.1055/s-2008-1045699.
10. Barry Lee W, Gotay A. Bilateral acanthamoeba keratitis in synergeyes contact lens wear: clinical and confocal microscopy findings. *Eye Contact Lens*. 2010. https://doi.org/10.1097/ICL.0b013e3181db3508.
11. Kim EC, Kim MS. Bilateral acanthamoeba keratitis after orthokeratology. *Cornea*. 2010;29(6):680–682. https://doi.org/10.1097/ICO.0b013e3181861bf9.
12. Biavasco F, Tittarelli R, Bertelli E, Frongia GB, Mariotti C. Bilateral acanthamoeba keratitis in a gas-permeable contact lens wearer. *Ophthalmologica*. 1994. https://doi.org/10.1159/000310530.
13. Voyatzis G, McElvanney A. Bilateral Acanthamoeba keratitis in an experienced two-weekly disposable contact lens wearer. *Eye Contact Lens*. 2007. https://doi.org/10.1097/01.icl.0000252567.06446.7b.
14. Muto T, Ishibashi Y. Three cases of bilateral Acanthamoeba keratitis. *J Jpn Ophthalmol Soc*. 2000. https://doi.org/10.1016/s0021-5155(00)00376-2.
15. Rama P, Matuska S, Viganò M, Spinelli A, Paganoni G, Brancato R. Bilateral Acanthamoeba keratitis with late recurrence of the infection in a corneal graft: a case report. *Eur J Ophthalmol*. 2003. https://doi.org/10.1177/112067210301300312.
16. Fathallah A, Ben Rayana N, Knani L, et al. Acanthamoeba keratitis. Report of 3 cases diagnosed in central Tunisia. *Tunis Med*. 2010;88(2):111–115. PMID: 20415171.
17. Colin J, Aitali F, Malet F, Touboul D, Feki J. Bilateral infectious keratitis in a patient wearing cosmetic soft contact lenses. *J Fr Ophtalmol*. 2006. https://doi.org/10.1016/S0181-5512(06)73829-3.
18. Maycock NJR, Jayaswal R. Update on acanthamoeba keratitis. *Cornea*. 2016. https://doi.org/10.1097/ico.0000000000000804.
19. Höllhumer R, Keay L, Watson SL. Acanthamoeba keratitis in Australia: demographics, associated factors, presentation and outcomes: a 15-year case review. *Eye*. 2019. https://doi.org/10.1038/s41433-019-0589-6.
20. Daas L, Szentmáry N, Eppig T, et al. Erratum: the German Acanthamoeba keratitis register: initial results of a multicenter study. *Ophthalmologe*. 2015;112:752–763. https://doi.org/10.1007/s00347-014-3225-7. Ophthalmologe. 2015. doi:10.1007/s00347-015-0144-1.
21. Kwok PWR, Kam KW, Jhanji V, Young AL. Painless acanthamoeba keratitis with normal vision. *Optom Vis Sci*. 2017. https://doi.org/10.1097/OPX.0000000000001023.
22. Tabin G, Taylor H, Snibson G, Murchison A, Gushchin A, Rogers S. Atypical presentation of Acanthamoeba keratitis. *Cornea*. 2001. https://doi.org/10.1097/00003226-200110000-00017.
23. Hsieh WC, Dornic DI. Acanthamoeba dendriform keratitis. *J Am Optom Assoc*. 1989;60(1):32–34. PMID: 2915106.
24. Gupta N, Samantaray JC, Duggal S, Srivastava V, Dhull CS, Chaudhary U. Acanthamoeba keratitis with Curvularia co-infection. *Indian J Med Microbiol*. 2010. https://doi.org/10.4103/0255-0857.58736.
25. Sharma R, Jhanji V, Satpathy G, Sharma N, Khokhar S, Agarwal T. Coinfection with acanthamoeba and pseudomonas in contact lens-associated keratitis. *Optom Vis Sci*. 2013. https://doi.org/10.1097/OPX.0b013e31827f15b4.
26. Gajdatsy AD, Kosmin A, Barrett GD. Coexistent adenoviral keratoconjunctivitis and Acanthamoeba keratitis. *Clin Exp Ophthalmol*. 2000. https://doi.org/10.1046/j.1442-9071.2000.00352.x.
27. Keratitis CA, Mathers HKWD, Goldberg MA, Sutphin JE, Dithqff JW, Folberg R. Coexistent Acanthamoeba keratitis and herpetic keratitis. *Arch Ophthalmol*. 1997. https://doi.org/10.1001/archopht.1997.01100150716002.
28. Moshirfar M, Hazin R, Khalifa YM. Central toxic keratopathy. *Curr Opin Ophthalmol*. 2010. https://doi.org/10.1097/ICU.0b013e32833a8cb2.
29. Sonmez B, Maloney RK. Central toxic keratopathy: description of a syndrome in laser refractive surgery. *Am J Ophthalmol*. 2007. https://doi.org/10.1016/j.ajo.2006.11.019.
30. Ting DSJ, Ghosh S. Central toxic keratopathy after contact lens wear and mechanical debridement: clinical characteristics, and visual and corneal tomographic outcomes. *Eye Contact Lens*. 2019. https://doi.org/10.1097/ICL.0000000000000575.
31. Hsu M, Tu E, Bouchard C. Confocal microscopy of contact lens keratitis presenting as central toxic keratopathy. *Eye Contact Lens*. 2011. https://doi.org/10.1097/ICL.0b013e31821c0401.
32. Moshirfar M, Kurz C, Ghajarnia M. Contact lens-induced keratitis resembling central toxic keratopathy syndrome. *Cornea*. 2009. https://doi.org/10.1097/ICO.0b013e318197ec3a.
33. Wagh VK, De Benito-Llopis L, O'Brart DPS. Idiopathic stromal keratitis resembling central toxic keratopathy. *J Cataract Refract Surg*. 2015. https://doi.org/10.1016/j.jcrs.2015.06.001.
34. Lakhani BK, Thajudeen B, Jawaid I, Attzs MS, Maharajan VS. Endotheliitis-A presentation of acanthamoeba keratitis. *Cornea*. 2021;40(6):769–773. https://doi.org/10.1097/ICO.0000000000002491.
35. Wilhelmus KR. Diagnosis and management of herpes simplex stromal keratitis. *Cornea*. 1987. https://doi.org/10.1097/00003226-198706040-00011.
36. Beigi B, Algawi K, Foley-Nolan A, O'Keefe M. Herpes simplex keratitis in children. *Br J Ophthalmol*. 1994. https://doi.org/10.1136/bjo.78.6.458.
37. Raghavan A, Veerappan S, Rangarajan V, et al. Fulminant acanthamoeba endophthalmitis after cataract surgery - a case report. *Cornea*. 2020;39(8):1055–1058. https://doi.org/10.1097/ICO.0000000000002289.
38. Ferreira CS, Figueira L, Moreira-Gonçalves N, Moreira R, Torrão L, Falcão-Reis F. Clinical and microbiological profile of bacterial microbial keratitis in a Portuguese tertiary referral center-where are we in 2015? *Eye Contact Lens*. 2018. https://doi.org/10.1097/ICL.0000000000000298.
39. Hsu C-C. Dendrite-like anterior stromal keratitis coinfected with Acanthamoeba and Pseudomonas in an orthokeratology contact lens wearer. *Taiwan J Ophthalmol*. 2019;9(2):131–133. https://doi.org/10.4103/tjo.tjo_114_17.
40. Mahmoudi S, Masoomi A, Ahmadikia K, et al. Fungal keratitis: an overview of clinical and laboratory aspects. *Mycoses*. 2018. https://doi.org/10.1111/myc.12822.
41. Goh JWY, Harrison R, Hau S, Alexander CL, Tole DM, Avadhanam VS. Comparison of in vivo confocal microscopy, PCR and culture of corneal scrapes in the diagnosis of acanthamoeba keratitis. *Cornea*. 2018;37(4):480–485. https://doi.org/10.1097/ICO.0000000000001497.
42. Wang SS, Feldman HA. Isolation of hartmannella species from human throats. *N Engl J Med*. 1967. https://doi.org/10.1056/NEJM196711302772204.
43. Cerva L. Acanthamoeba culbertsoni and Naegleria fowleri: occurrence of antibodies in man. *J Hyg Epidemiol Microbiol Immunol*. 1989;33(1):99–103.
44. Lau R, Cunanan M, Jackson J, et al. Reevaluation of an acanthamoeba molecular diagnostic algorithm following an atypical case of amoebic keratitis. *J Clin Microbiol*. 2015. https://doi.org/10.1128/JCM.01607-15.
45. Tu EY, Joslin CE, Sugar J, Booton GC, Shoff ME, Fuerst PA. The relative value of confocal microscopy and superficial corneal scrapings in the diagnosis of acanthamoeba keratitis. *Cornea*. 2008;27(7):764–772. https://doi.org/10.1097/ICO.0b013e31816f27bf.
46. Alkatan HM, Al-Essa RS. Challenges in the diagnosis of microbial keratitis: a detailed review with update and general guidelines. *Saudi J Ophthalmol*. 2019. https://doi.org/10.1016/j.sjopt.2019.09.002.
47. Sagoo MS, Mehta JS, Hau S, et al. Microsporidium stromal keratitis: in vivo confocal findings. *Cornea*. 2007;26(7):870–873. https://doi.org/10.1097/ICO.0b013e31806c7a3c.
48. Hadden OB, McGhee CNJ, Morris AT, Gray TB, Ring CP, Watson ASJ. Outbreak of diffuse lamellar keratitis caused by marking-pen toxicity. *J Cataract Refract Surg*. 2008. https://doi.org/10.1016/j.jcrs.2008.03.024.
49. Marí Cotino JF, Suriano MM, De La Cruz Aguiló RI, Vila-Arteaga J. Central toxic keratopathy: a clinical case series. *Br J Ophthalmol*. 2013. https://doi.org/10.1136/bjophthalmol-2012-302732.
50. Chen HT, Chen KH, Hsu WM. Toxic keratopathy associated with abuse of low-dose anesthetic: a case report. *Cornea*. 2004. https://doi.org/10.1097/01.ico.0000114127.63670.06.