Case Report

Vortex keratopathy after photorefractive keratectomy in a patient on long-term clozapine treatment

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ABSTRACT

Background: Vortex keratopathy is a corneal entity characterized by corneal deposits at the level of the basal epithelium in the form of a whorl-like pattern in the interpalpebral portions of the cornea. Medications such as amiodarone, chloroquine, hydroxychloroquine, indomethacin, phenothiazines, ibuprofen, and naproxen bind to the cellular lipids of the basal epithelial layer of the cornea, producing a characteristic whorl pattern. Here, we report a case of bilateral central vortex keratopathy with slight vision impairment 3 weeks after uneventful photorefractive keratectomy (PRK) in a woman on long-term clozapine treatment.

Case Presentation: A 42-year-old woman presented to the outpatient clinic for refractive surgery for the correction of bilateral moderate myopia. Her best-corrected distance visual acuity was 20 / 20 in both eyes. She had been on antipsychotic clozapine tablets 400 mg / day for the past 6 years to manage a psychiatric disorder. On detailed preoperative slit-lamp examination, her corneas were clear, with perilimbal conjunctival pigmentations. Other ocular examination results were unremarkable. At the 3-week follow-up after an uneventful PRK, her uncorrected distance visual acuity was 20 / 25 in the right eye and 20 / 20 in the left eye, with complaints of slightly unclear vision in both eyes. Slit-lamp examination revealed bilateral corneal subepithelial deposits in a whorl-like pattern reminiscent of vortex keratopathy. The deposits were restricted to the epithelial and subepithelial regions and did not extend to the stroma without evident stromal haze. Dilated fundus examination results were normal bilaterally. Despite excellent refractive outcomes and visual acuity in both eyes, she was dissatisfied and complained of unclear vision. She was administered with lubricating eye drops and placed on regular follow-ups. At the 4-month follow-up, the vortex lines were cleared centrally, and she reported improvement in vision. Anterior-segment optical coherence tomography of the cornea revealed no epithelial deposits in the central part of the cornea and residual deposits in the temporal peripheral cornea, indicating clearing of the deposits from the central cornea and explaining the subjective improvement in vision. Her final best-corrected distance visual acuity was 20 / 20 in both eyes with an unremarkable ocular examination.

Conclusions: Our case indicates a potential causal relationship between long-term clozapine treatment and development of temporary, visually significant vortex keratopathy after uneventful PRK. Further large-scale studies are required to verify the causal relationship between the long-term clozapine administration and the development of vortex keratopathy following surface ablation photorefractive procedures.

KEYWORDS

photorefractive keratectomies, visual acuities, vortex keratopathy, optical coherence tomography, clozaril, side effects, corneas, conjunctivas

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How to cite this article: Shoughy S, Elgemie H, Nasif W. Vortex keratopathy after photorefractive keratectomy in a patient on long-term clozapine treatment. Med Hypothesis Discov Innov Optom. 2022 Winter; 3(4): 160-164. https://doi.org/10.51329/mehdioptometry165

Received: 24 October 2022; Accepted: 26 December 2022

INTRODUCTION

Vortex keratopathy is a condition characterized by corneal deposits at the level of the basal epithelium in a whorl-like pattern of golden-yellow or gray deposits in the interpalpebal portions of the cornea [1, 2]. Several medications bind to the cellular lipids of the basal epithelial layer of the cornea, producing the characteristic whorl pattern, with amiodarone being the most common [1]. This pattern can be caused by other drugs that are mostly cationic amphiphilic, including chloroquine, hydroxychloroquine, indomethacin, phenothiazines, ibuprofen, and naproxen; systemic diseases such as Fabry disease and multiple myeloma; or genetic causes such as Meesmann corneal dystrophy, in which diffuse epithelial cysts can exhibit the vortex pattern [1, 2]. Generally, subepithelial deposits of vortex keratopathy do not interfere with vision; however, some patients may experience impairment of visual acuity or other visual symptoms [3].

Clozapine is an antipsychotic drug with cationic amphiphilic properties [4, 5]. It is a commonly used antipsychotic drug successfully used to treat refractory psychosis. However, its use is associated with various systemic adverse effects [6]. Long-term treatment with clozapine induces ocular side effects, including dry eye syndrome, pigmentary changes affecting the cornea and retina, and stellate cataract [7-9]. The etiology of clozapine-related ocular side effects remains unclear. However, as clozapine is a tricyclic dibenzodiazepine with dopamine-receptor blocking properties, it may lead to altered dopaminergic regulation of melatonin, leading to ocular pigmentary changes and development of cataract [9].

No case of laser-based refractive surgery has been reported in a patient with Fabry disease [10]. However, a case of uneventful laser in situ keratomileusis (LASIK) after partial limbal stem cell deficiency secondary to contact lens overwear in a patient with whorl epitheliopathy resembling Fabry verticillata has been reported. Postoperatively, the patient's uncorrected visual acuity reached 20/15 in both eyes, with no recurrence of signs or symptoms of limbal stem cell deficiency in either eye [11]. Moreover, bilateral central vortex keratopathy occurred 5 years after an uneventful LASIK in a 45-year-old man with complaints of reduced vision and temporary bilateral blurred vision, particularly when driving. The patient had been receiving amiodarone for atrial fibrillation for approximately 2 years [12].

Here, we report a case of bilateral central vortex keratopathy with slight vision impairment 3 weeks after uneventful photorefractive keratectomy (PRK) for myopic correction in a woman with a history of psychiatric disorder for which she was on long-term clozapine treatment.

CASE PRESENTATION

A 42-year-old woman presented to the outpatient clinic who was keen for refractive surgery for correction of bilateral moderate myopia. Her best-corrected distance visual acuity was 20 / 20 in both eyes measured using an automatic chart projector (PACP-7000/PACP-7000L, Potec Co., Ltd., Dong-gu, Korea). She had been taking antipsychotic clozapine tablets 400 mg / day for 6 years to manage a psychiatric disorder. Other than that, her full history, including general medical, family, ocular, and surgical histories, was unremarkable. Further, she had no history of phenothiazine use.

Her extraocular muscle movements appeared normal with a full range of motion, and she had no gross ocular misalignment or diplopia. The Schirmer test results were within the normal range for both eyes [13]. On detailed preoperative anterior segment examination under a slit-lamp microscope (SL-2G; Topcon Co., Tokyo, Japan), her corneas were clear; anterior chambers were deep and quiet; pupils were round, regular, reactive, without the afferent pupillary defect; lenses were clear with no obvious pigmentary deposits or opacity; and bilateral perilimbal conjunctival pigmentations were found. Fundus examination using a slit-lamp microscope with a noncontact + 90 D Volk lens (Volk Optical, Inc, Mentor, OH, USA) was normal with no obvious retinal pigmentary changes. Cycloplegic refraction was performed after instilling two drops of 1% cyclopentolate (Cyclogyl; Alcon Laboratories Inc.) using a streak retinoscope (HSR II; Heine Optotechnik, Herrsching, Germany). Her refractive error was - 2.00 diopters spherical bilaterally with no cylinder component of refraction. Corneal topography (Orbscan, Bausch and Lomb Inc., Rochester, NY, USA) showed normal patterns.

The patient underwent uneventful PRK for myopic correction under topical anesthesia. The epithelium was mechanically removed, followed by application of an excimer laser, as detailed elsewhere [14]. PureVision bandage contact lenses (Bausch & Lomb, Rochester, NY, USA) were placed on the eyes after completion of surgery. Postoperatively, the patient was prescribed with artificial tear (Optive; Allergan, Irvine, CA, USA) eye drops six times / day for 3 months. After removal of bandage contact lenses, on postoperative day 4, the fluorometholone ophthalmic solution (FML, Allergan) was administered four times / day and tapered over 1 month. The patient was examined 24 h postoperatively. On slit-lamp examination, the corneas were clear, and soft contact lenses were in place. On postoperative day 4, soft contact lenses were removed, and ocular examination revealed quiet eyes with clear corneas.

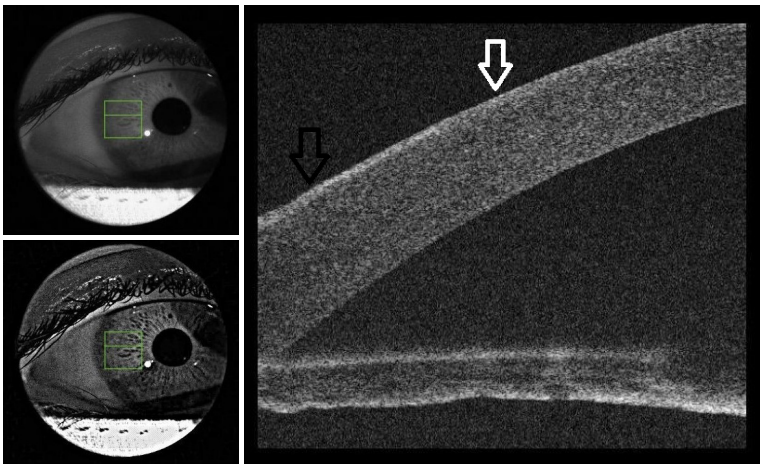

Figure 1. Anterior-segment optical coherence tomography (AS-OCT; Triton, Swept Source, Topcon Inc., Tokyo, Japan) scan of the right cornea of the patient following improvement of her visual acuity shows the absence of epithelial deposits in the central part of the cornea, seen as the absence of hyperreflectivity in this area (white arrow) and residual deposits in the temporal peripheral cornea, seen as hyperreflective materials above the Bowman membrane (black arrow).

At the 3-week follow-up after an uneventful PRK, her uncorrected distance visual acuity was 20 / 25 in the right eye and 20 / 20 in the left eye, with complaints of slightly unclear vision in both eyes. Slit-lamp examination revealed bilateral corneal subepithelial deposits in a whorl-like pattern, consistent with vortex keratopathy. The deposits were restricted to the epithelial and subepithelial regions and did not extend to the stroma, without evident stromal haze. Dilated fundus examination results were normal bilaterally. Despite excellent refractive outcomes and visual acuity in both eyes, the patient was dissatisfied and complained of unclear vision. She was administered with lubricating eye drops and placed on regular follow-ups.

At the 4-month follow-up, the vortex lines were cleared centrally on slit-lamp examination, and the patient reported improvement in vision. Anterior-segment optical coherence tomography (AS-OCT; Triton, Swept Source, Topcon Inc., Tokyo, Japan) of the cornea revealed no epithelial deposits in the central part of the cornea, seen as the absence of hyperreflectivity in this area, and residual deposits in the temporal peripheral cornea, seen as hyperreflective materials above the Bowman membrane (Figure 1), indicating clearing of the deposits from the central cornea and subjective improvement in vision. Her final best-corrected distance visual acuity was 20 / 20 in both eyes, with an unremarkable ocular examination.

The study protocol was approved by the institutional review board. The patient provided written informed consent for participation and publication of this case report.

DISCUSSION

The patient had been taking clozapine for 6 years. Preoperatively, she showed perilimbal conjunctival pigmentations, but without cataracts or retinal pigmentary changes. At the 3-week follow-up after an uneventful refractive surface ablation, she developed vortex keratopathy. The characteristic whorl-pattern was central, with extension to the whole quadrants of the cornea. Despite the optimum refractive outcome, the patient complained of slight vision impairment. This reduced clarity of vision is mostly related to the development of vortex keratopathy.

Corneal lesions in vortex keratopathy branch out from a central whorl, usually across the inferior cornea, as in patients on amiodarone [15]. However, the present patient developed central distribution of the vortex pattern. In another case, bilateral central vortex keratopathy was reported 5 years after an uneventful LASIK in a patient on amiodarone treatment for atrial fibrillation for approximately 2 years [12]. The central position of the vortex changes may have contributed to the reduced vision quality in the present patient.

Considering that clozapine is an antipsychotic drug with cationic amphiphilic properties [4, 5] and vortex keratopathy can be caused by drugs that are mostly cationic amphiphilic [1, 2], the development of vortex changes might be attributable to long-term clozapine use in the present case. However, owing to the lack of similar reports in the literature, large-scale studies on patients receiving long-term high-dose clozapine are required to verify this potential causal relationship.

Long-term phenothiazine use causes pigment deposits in the cornea. Since clozapine has a similar dopamine receptor-blocking property, it may lead to altered dopaminergic regulation of melatonin [9],

resulting in pigment deposits in the cornea [9]. These deposits may be clinically apparent because of the high rate of epithelial migration during healing of the corneal defect following PRK [16]. However, in the present patient, vortex keratopathy did not appear clinically up to postoperative day 4 when the epithelial defect healed completely and was noted 3 weeks postoperatively. This may be explained by the fact that epithelial cellular changes were initially minimal; therefore, we could not clinically detect them using slit-lamp biomicroscopy.

Ikegawa et al. found that pathological findings in cases of amiodaron-induced keratopathy were detected earlier using confocal microscopy than using slit-lamp biomicroscopy [17]. However, we did not perform preoperative or postoperative confocal microscopy in the present case to prove the presence of similar pathological findings. Changes in corneal morphology and tear film after refractive surgery [18-20] may have contributed to the later appearance of vortex keratopathy in the present case.

Ortega-Usobiaga et al., in a retrospective observational assessment of 33 eyes of 20 patients on amiodarone, found no significant clinical complications up to 3 months after LASIK or surface ablation [21]. The present patient might have had subclinical vortex pattern keratopathy before PRK because of the very slow rate of epithelial turnover; therefore, migrating cells could not be distinguished from surrounding non-migrating cells. After PRK, healing of the relatively large epithelial defect is achieved by a higher rate of migration of epithelial cells [16, 22], making the vortex pattern clinically apparent.

A case of ocular and skin pigmentation after long-term, high-dose (800 mg) clozapine treatment for schizophrenia has been reported. The patient developed pigmented deposits on the corneal endothelium and anterior central stellate cataract with bilateral pigmentary retinopathy. The patient's best-corrected visual acuity was reduced to 6 / 9 and 6 / 60 in the right and left eyes, respectively [7]. The present patient developed bilateral perilimbal conjunctival pigmentations on slit-lamp examination preoperatively, despite having apparently normal posterior-segment examination results preoperatively and postoperatively. These perilimbal conjunctival pigmentations might be evidence of side effects of long-term clozapine use due to pigment deposits in the conjunctiva.

Clozapine can cause neuro-ophthalmic toxicity, oculogyric crisis, anticholinergic syndrome, myopathy, and diplopia [23]. Kushner et al. reported the possibility of diplopia manifestation after refractive surgery and recommended preoperative screening criteria to minimize the incidence of this complication [24]. Predicting the binocular outcome and identification of risk factors should be considered for every refractive surgery candidate preoperatively [25, 26]. Despite long-term use of clozapine, the present patient developed normal extraocular muscle movements with a full range of motion and had no gross ocular misalignment or diplopia on preoperative examination. Similarly, postoperatively, she had no complaints attributable to binocular or accommodative abnormalities.

This case report, for the first time, suggests the likelihood of developing significant vortex keratopathy after uneventful PRK in a patient on long-term clozapine treatment for managing a psychiatric disorder. However, it is limited by the absence of strong evidence to prove this causal relationship. Large-scale studies with detailed preoperative clinical and paraclinical evaluations along with longer postoperative follow-ups are required to verify our assumption. Post-PRK aberrometry may be implicated in the future in such cases to differentiate between diminution of vision secondary to higher-order aberrations induced by vortex keratopathy.

CONCLUSIONS

The present case indicates a potential causal relationship between long-term clozapine treatment and the development of temporary, visually significant vortex keratopathy after uneventful PRK. Patients on long-term clozapine indicated for refractive surgery should be treated with caution, as this medication may predispose to the development of temporary visually significant vortex keratopathy in the cornea even after uneventful refractive surgery. Further studies supported by confocal microscopy and AS-OCT are required to clarify the exact pathological mechanisms underlying the development of vortex keratopathy in such cases. Moreover, large-scale studies are required to verify the causal relationship between long-term clozapine administration and the development of vortex keratopathy following surface ablation photorefractive procedures.

ETHICAL DECLARATIONS

Ethical approval: The study protocol was approved by the institutional review board. The patient provided written informed consent for participation and publication of this case report.
Conflict of interests: None

FUNDING

None.

ACKNOWLEDGMENTS

None.

REFERENCES

1. Raizman MB, Hamrah P, Holland EJ, Kim T, Mah FS, Rapuano CJ, et al. Drug-induced corneal epithelial changes. Surv Ophthalmol. 2017;62(3):286-301. doi: 10.1016/j.survophthal.2016.11.008 pmid: 27890620
2. Sahyoun JY, Sabeti S, Robert MC. Drug-induced corneal deposits: an up-to-date review. BMJ Open Ophthalmol. 2022;7(1):e000943. doi: 10.1136/bmjophth-2021-000943 pmid: 35415268
3. Hollander DA, Aldave AJ. Drug-induced corneal complications. Curr Opin Ophthalmol. 2004;15(6):541-8. doi: 10.1097/01.icu.0000143688.45232.15 pmid: 15523201
4. Gitahy Falcao Faria C, Weiner L, Petrignet J, Hingray C, Ruiz De Pellon Santamaria Á, Villoutreix BO, et al. Antihistamine and cationic amphiphilic drugs, old molecules as new tools against the COVID-19? Med Hypotheses. 2021;148:110508. doi: 10.1016/j.mehy.2021.110508 pmid: 33571758
5. Wolf K, Kühn H, Boehm F, Gebhardt L, Glaudo M, Agelopoulos K, et al. A group of cationic amphiphilic drugs activates MRGPRX2 and induces scratching behavior in mice. J Allergy Clin Immunol. 2021;148(2):506-522.e8. doi: 10.1016/j.jaci.2020.12.655 pmid: 33617860
6. Wu MK, Chung W, Wu CK, Tseng PT. The severe complication of Stevens-Johnson syndrome induced by long-term clozapine treatment in a male schizophrenia patient: a case report. Neuropsychiatr Dis Treat. 2015;11:1039-41. doi: 10.2147/NDT.S79327 pmid: 25914536
7. Borovik AM, Bosch MM, Watson SL. Ocular pigmentation associated with clozapine. Med J Aust. 2009;190(4):210-1. doi: 10.5694/j.1326-5377.2009.tb02353.x pmid: 19220190
8. Ceylan E, Ozer MD, Yilmaz YC, Kartal B, Yildiz Ekinci D, Çinici E, et al. The ocular surface side effects of an anti-psychotic drug, clozapine. Cutan Ocul Toxicol. 2016;35(1):62-6. doi: 10.3109/15569527.2015.1018387 pmid: 25853177
9. Alam MS, Praveen Kumar KV. Clozapine-induced cataract in a young female. J Pharmacol Pharmacother. 2016;7(4):184-186. doi: 10.4103/0976-500X.195904 pmid: 28163541
10. Moshirfar M, Bundogji N, Tukan AN, Ronquillo YC. Implications of Corneal Refractive Surgery in Patients with Fabry Disease. Ophthalmol Ther. 2022;11(3):925-929. doi: 10.1007/s40123-022-00503-0 pmid: 35438438
11. Lim L, Wei RH. Laser in situ keratomileusis treatment for myopia in a patient with partial limbal stem cell deficiency. Eye Contact Lens. 2005;31(2):67-9. doi: 10.1097/01.icl.0000146302.00152.47 pmid: 15798476
12. Schroeder FM, Hörle S. Zentrale Cornea verticillata nach Lasik bei Amiodaron-Therapie [Vortex keratopathy with unusual central position after LASIK-treatment with amiodarone]. Klin Monbl Augenheilkd. 2009;226(1):66-7. German. doi: 10.1055/s-2008-1027841 pmid: 19173166
13. Karampatakis V, Karamitsos A, Skriapa A, Pastiadis G. Comparison between normal values of 2- and 5-minute Schirmer test without anesthesia. Cornea. 2010;29(5):497-501. doi: 10.1097/ICO.0b013e3181c2964c pmid: 20299972
14. El-Sersy TH. Assessment of posterior corneal surface changes after photorefractive keratectomy in moderate myopia. Journal of the Egyptian Ophthalmological Society. 2016;109(4):167-171. doi: 10.4103/2090-0686.204728
15. Turk U, Turk BG, Yılmaz SG, Tuncer E, Alioğlu E, Dereli T. Amiodarone-induced multiorgan toxicity with ocular findings on confocal microscopy. Middle East Afr J Ophthalmol. 2015;22(2):258-60. doi: 10.4103/0974-9233.154411 pmid: 25949090
16. Tomás-Juan J, Murueta-Goyena Larrañaga A, Hanneken L. Corneal Regeneration After Photorefractive Keratectomy: A Review. J Optom. 2015;8(3):149-69. doi: 10.1016/j.optom.2014.09.001 pmid: 25444646
17. Ikegawa Y, Shiraishi A, Hayashi Y, Ogimoto A, Ohashi Y. In Vivo Confocal Microscopic Observations of Vortex Keratopathy in Patients with Amiodarone-Induced Keratopathy and Fabry Disease. J Ophthalmol. 2018;2018:5315137. doi: 10.1155/2018/5315137 pmid: 29750121
18. Nejima R, Miyata K, Tanabe T, Okamoto F, Hiraoka T, Kiuchi T, et al. Corneal barrier function, tear film stability, and corneal sensation after photorefractive keratectomy and laser in situ keratomileusis. Am J Ophthalmol. 2005;139(1):64-71. doi: 10.1016/j.ajo.2004.08.039 pmid: 15652829
19. Jung JW, Kim JY, Chin HS, Suh YJ, Kim TI, Seo KY. Assessment of meibomian glands and tear film in post-refractive surgery patients. Clin Exp Ophthalmol. 2017;45(9):857-866. doi: 10.1111/ceo.12993 pmid: 28544605
20. Rosa N, Borrelli M, De Bernardo M, Lanza M. Corneal morphological changes after myopic excimer laser refractive surgery. Cornea. 2011;30(2):130-5. doi: 10.1097/ICO.0b013e3181f237a1 pmid: 21045644
21. Ortega-Usobiaga J, Llovet-Osuna F, Reza Djodeyre M, Cobo-Soriano R, Llovet-Rausell A, Baviera-Sabater J. LASIK and surface ablation in patients treated with amiodarone. Arch Soc p Oftalmol. 2016;91(11):520-525. English, Spanish. doi: 10.1016/j.oftal.2016.05.005 pmid: 27350387
22. Reynolds A, Moore JE, Naroo SA, Moore CB, Shah S. Excimer laser surface ablation - a review. Clin Exp Ophthalmol. 2010;38(2):168-82. doi: 10.1111/j.1442-9071.2010.02230.x pmid: 20398106
23. Jain KK (2021). 'Drug-induced neurological disorders'. Springer Nature; 4th edn (pp. 413-496). Publisher: Springer Cham. eBook ISBN: 978-3-030-73503-6. doi: 10.1007/978-3-030-73503-6
24. Kushner BJ, Kowal L. Diplopia after refractive surgery: occurrence and prevention. Arch Ophthalmol. 2003;121(3):315-21. doi: 10.1001/archopht.121.3.315 pmid: 12617699
25. Finlay AL. Binocular vision and refractive surgery. Cont Lens Anterior Eye. 2007;30(2):76-83. doi: 10.1016/j.clae.2007.02.009 pmid: 17448926
26. García-Montero M, Albarrán Diego C, Garzón-Jiménez N, Pérez-Cambrodí RJ, López-Artero E, Ondategui-Parra JC. Binocular vision alterations after refractive and cataract surgery: a review. Acta Ophthalmol. 2019;97(2):e145-e155. doi: 10.1111/aos.13891 pmid: 30218490