American Journal of Ophthalmology Case Reports 37 (2025) 102235

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

A case of corneal opacity caused by atovaquone administration

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ARTICLE INFO

Keywords:
Atovaquone
Corneal opacity

ABSTRACT

Purpose: Atovaquone is an alternative drug that is used for the prevention and treatment of *Pneumocystis* pneumonia when the first-line drug, sulfamethoxazole-trimethoprim (ST combination), cannot be used due to side effects. However, atovaquone is known to cause ocular side effects including oculomucocutaneous syndrome and vortex keratopathy. In this report, we describe a patient who developed bilateral white granular diffuse corneal opacity that extended from the corneal sub-epithelium to the stroma after continuous oral atovaquone administration for 14 months.

Observations: The patient was a 15-year-old male with no prior ophthalmological or family medical history, but with a medical history of aplastic anemia treatment at our hospital's pediatric department. Examination showed bilateral diffuse white granular corneal opacity that extended from the sub-epithelium to the stroma, with no other abnormalities in the anterior and posterior segments of both eyes.

Conclusions and importance: We encountered a rare case of bilateral corneal opacity resulting from oral atovaquone administration. Regular long-term ophthalmological examinations are necessary for patients taking atovaquone.

1. Introduction

Atovaquone is a prophylactic and therapeutic drug used for *Pneumocystis* pneumonia. This drug was approved in Japan in 2012, as it is easier to use and considered to have fewer side effects compared to the use of the first-line drug, sulfamethoxazole-trimethoprim (ST combination), and pentamidine. However, this drug is not as effective as the other two agents.[1,2] Atovaquone is a bright yellow suspension with a fruity aroma, with the recommended dosage for the treatment of *Pneumocystis* pneumonia stated to be 5 mL (750 mg of atovaquone) twice a day for 21 days, while for prevention, the administered dose is 10 mL (1500 mg of atovaquone) orally once a day after meals. Atovaquone works by inhibiting the mitochondrial electron transport chain (mitochondrial respiratory chain) complex III of *Pneumocystis carinii* (*Pneumocystis jirovecii* derived from rat). Atovaquone exhibits anti-*Pneumocystis jirovecii* activity by inhibiting the binding of the mitochondrial inner membrane protein ubiquinone to cytochrome *b* (a component of complex III), which results in a significant decrease in the adenosine triphosphate levels and subsequent anti-*Pneumocystis* activity. Atovaquone's known side effects include oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, severe liver dysfunction, agranulocytosis, and leukopenia, although their frequency remains unknown. In 1995, one case of bilateral corneal vortex opacity due to atovaquone administration was reported.[3]

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.[4] After we conducted a literature review in 2023 that utilized PubMed and Google Scholar using the keywords "cornea" and "corneal opacity", we could not find any prior reports regarding atovaquone deposits in the corneal stroma. Herein, we report a case of corneal opacity with stromal deposit that occurred while taking atovaquone.

2. Case report

This case involved a 15-year-old male with no family history of corneal dystrophy.

The patient had a medical history of aplastic anemia and was currently being treated in the pediatric department of our hospital. In 2022, the patient experienced blurred vision in both eyes while exercising. Two days later, he visited a local ophthalmology clinic, where diffuse bilateral corneal opacity was noted. As a result, he was referred

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https://doi.org/10.1016/j.ajoc.2024.102235
Received 6 June 2024; Received in revised form 21 November 2024; Accepted 7 December 2024
Available online 12 December 2024

to our department for further investigation and treatment.

Initial examination findings included a best-corrected visual acuity (BCVA) of 20/16 in the right eye (OD) and 20/32 in the left eye (OS). The refractive error was −0.5–0.75/169 for the OD and +2.00–1.50/10 for the OS. Intraocular pressure measured by applanation tonometry was 21 and 20 mmHg in OD and OS, respectively. Diffuse white granular corneal opacity was observed in both eyes, extending from the subepithelial layer to the stroma. The diffuse opacity was evenly distributed throughout the cornea and did not resemble a vortex keratopathy (Fig. 1A–F). Except for the cornea, no abnormalities were observed in either eye in the anterior or posterior segments. There were no inflammatory findings such as keratic precipitates, inflammatory cells, fibrin deposition, vitreous opacity, bleeding, or congestion observed in the anterior, or posterior segments. Anterior segment optical coherence tomography (OCT) showed there was no change in the corneal shape and the opacity was uniformly diffuse throughout both corneas (Fig. 2A–B). In vivo confocal microscopy was subsequently performed and showed corneal stromal pigmentation (Fig. 3).

At the initial visit, the cause of the corneal opacity was suspected to be either familial or drug-induced. However, there was no family history of corneal dystrophy, and an evaluation of his father, who had accompanied him to the examination, found no similar findings. After evaluating the patient's medication history, it was discovered that he was taking cyclosporine (50 mg/day) and atovaquone (1500 mg/day). Therefore, we suspected the possibility of drug-induced corneal opacity caused by the atovaquone. As a result, one month after the first visit to our department, we discontinued the drug after consulting with a pediatric physician.

Treatment history at the pediatric department of our hospital indicated that the patient had been administered an oral ST combination drug 14 months previous, in order to prevent *Pneumocystis* pneumonia during his treatment for aplastic anemia. However, due to the appearance of a skin rash about one month later, the ST combination drug was discontinued. The ST combination drug was replaced with atovaquone. After 14 months of atovaquone administration, the patient developed blurred vision in both eyes, which led to him visiting his local ophthalmology clinic. The total dose of atovaquone that was administered was 655,500 mg (1500 mg/day × 437 days).

One year after discontinuing atovaquone, although there was an improvement noted in the unaided visual acuity, there was no significant change observed in the corneal opacity of both eyes (Fig. 1G–H and Fig. 2C–D). Although the subjective symptoms of blurred vision exhibited a slight improvement, the corneal stromal opacities persisted.

Regarding genetic disorders, the results of chromosome fragility tests, telomere length measurements, and genetic tests related to hematopoietic insufficiency did not indicate the possibility of hereditary hematopoietic insufficiency syndrome. While genetic testing for corneal dystrophy has not been conducted, it is unlikely that this is the cause, as there is no family history of the disease.

3. Discussion

Atovaquone-induced keratopathy was initially reported in 1995 by Shah et al.[3] In this reported case, while the patient presented with vortex keratopathy, it was without any deposition in the corneal stroma. In contrast to the findings that have been previously reported for this drug, we found that atovaquone affected the corneal stroma.[3]

Slit-lamp examination revealed there was a diffuse white granular corneal opacity that was similar to that reported for amiodarone and chloroquine, which are known to cause granular white-grey opacities that are diffusely distributed throughout the entire cornea.[5,6]

Atovaquone is a lipophilic substance that shares similarities with amiodarone and chloroquine. This suggests that atovaquone may also cause corneal stromal deposition through the same mechanism as that found for amiodarone. Histologically, this deposition has been reported to be caused by the accumulation of drug-lipid complexes.[5] Amiodarone reaches the cornea via the tear film, aqueous humor, and limbal vasculature. The drug or its metabolites penetrate lysosomes and bind with cellular lipids, producing drug-induced lipidosis. It has also been shown that endocytosis of the drug-protein complex occurs, and that this is concentrated in the cornea.[3]

Certain drugs, such as atovaquone, amiodarone, and chloroquine, are known to have a unique structure that is referred to as cationic amphiphilic. This structure consists of a hydrophobic ring and a hydrophilic cationic amine side chain, which allows these drugs to pass through the cell membrane. As a result, when these drugs enter the cells, they can cause an accumulation of phospholipids, which leads to a condition known as vortex keratopathy.[6]

Other drugs that can cause vortex keratopathy, which affects only the epithelium, include hydroxychloroquine, phenothiazines, tamoxifen, indomethacin, gentamicin (subconjunctival administration), perhexiline maleate, suramin, ibuprofen, chlorpromazine, and cationic

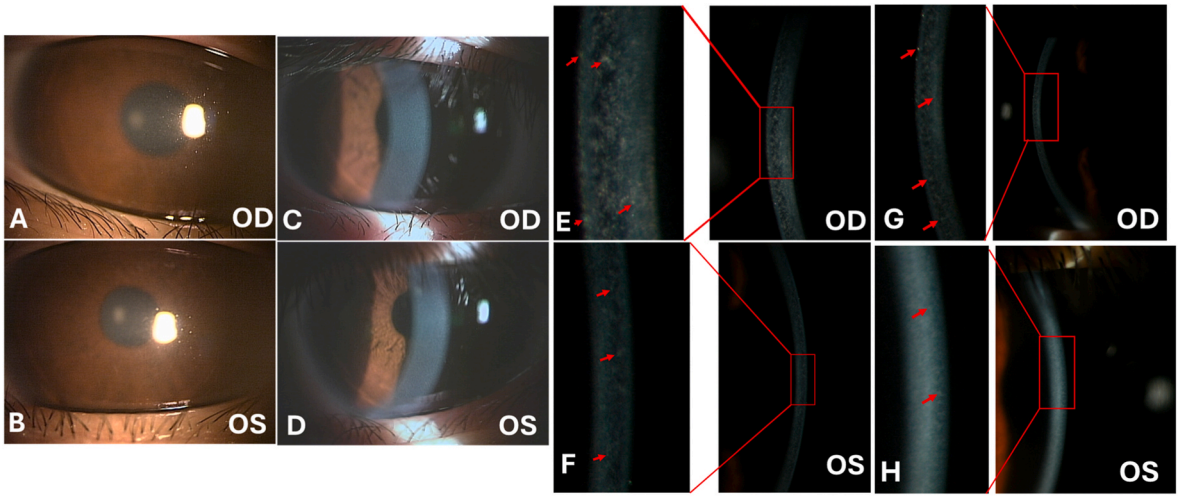

Fig. 1. A 15-year-old boy with aplastic anemia complained of blurry vision bilaterally after using oral atovaquone for 14 months. (A, B, C, and D): slit lamp examination during the patient's first visit showed diffuse bilateral corneal opacities. (E and F): slit-lamp examination with magnified insets for both eyes show corneal opacity. The opacity was diffuse and extended from the corneal epithelium to the stroma. Arrows in the magnified insets show a sample of deposits and opacities in different locations in both corneas. (G and H) Slit lamp examination after 1 year of discontinuing atovaquone, shows bilateral remaining opacities despite improvement noted in the unaided visual acuity. OD = right eye and OS = left eye.

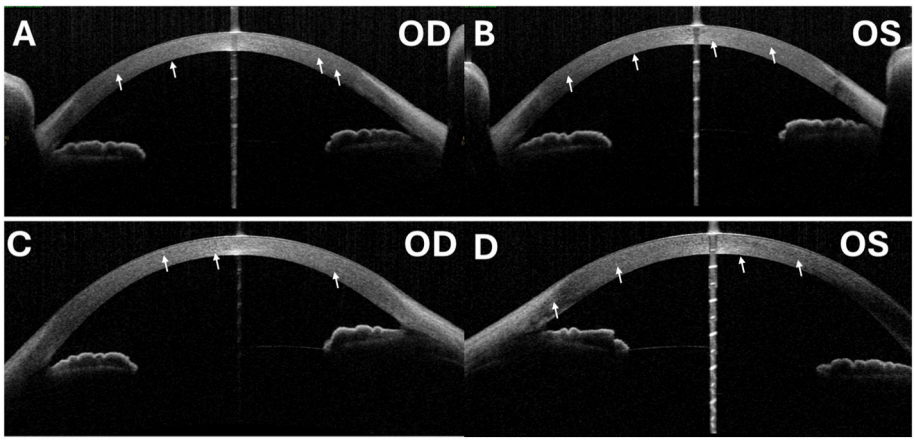

Fig. 2. A 15-year-old boy with aplastic anemia complained of blurry vision bilaterally after using oral atovaquone for 14 months. (A and B): Anterior segment OCT shows no change in the corneal shape for both eyes. Corneal opacity (white arrows) was not localized but was uniformly observed throughout the corneal stroma. (C and D) Anterior segment OCT shows remaining corneal opacities in both eyes after 1 year of stopping the use of atovaquone. OCT = Optical Coherence Tomography.

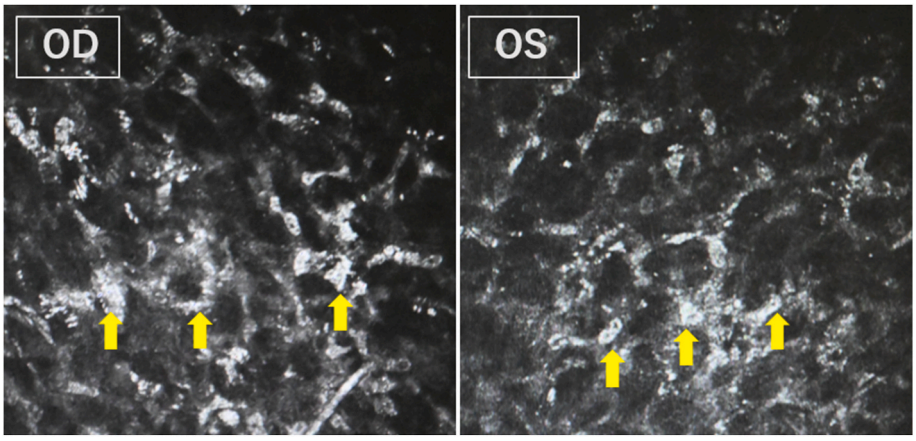

Fig. 3. A 15-year-old boy with aplastic anemia complained of blurry vision bilaterally after using oral atovaquone for 14 months. The in vivo confocal microscopy images, which were observed 7 months after the onset of the symptoms, show pigmentation in the corneal stroma.

amphiphilic drugs.[6] Diseases associated with vortex keratopathy include Fabry disease, multiple myeloma, and radial keratopathy (post-radial keratotomy).[6] In addition, there are several drugs that can cause corneal deposition and opacity in the epithelium, the stroma of the cornea, or in both areas. These drugs include chlorpromazine, rifabutin, clofazimine, isotretinoin, vandetanib, suramin, indomethacin, tamoxifen and gold salts.[5] However, the present case had not been previously prescribed any of these drugs nor had he had any of the diseases that can potentially cause keratopathy.

Corneal infiltrates are caused by various causes, including infectious and sterile causes. Infectious causes can include viruses, bacteria, and, less commonly, fungi and protozoa. Sterile causes include contact lens usage, autoimmune diseases, vernal keratoconjunctivitis, and iatrogenic issues, such as corneal surgery.[7,8] We excluded these due to the absence of any signs of inflammation in the cornea, conjunctiva, and anterior chamber.

Genetic diseases like de novo mutations (DNMs) need to be considered in such cases. Although we did not perform genetic testing for DNMs for the corneal dystrophies, we believe that this is unlikely given the lack of any family history and the sporadic nature of the condition.

Furthermore, regardless of the type of the corneal deposit, drug cessation or modification can potentially be helpful in the treatment of the corneal opacity caused by this drug. However, these actions need to be weighed against the potential systemic risks. Some drug-induced corneal opacities, such as those caused by chlorpromazine, rifabutin, and indomethacin, may potentially improve after treatment discontinuation. In contrast, it has been reported that others, such as raloxifene-induced keratopathy and atovaquone-induced keratopathy, may not improve even after the drug is discontinued.[5,6,9,10] The symptoms of decreased vision were mild, and the subjective symptoms slightly improved in conjunction with the cessation of atovaquone. Therefore, surgical treatments such as lamellar corneal transplantation or full-thickness corneal transplantation were not indicated. Surgical intervention, such as deep anterior lamellar keratoplasty, may be necessary if active corneal scars are detected or if there is a worsening of corneal stromal opacity. Therefore, the management of drug-induced corneal opacities needs to be individualized based on the specific medication and its associated risks and benefits.[5,6]

In the present case, the typical vortex keratopathy did not occur. This was thought to be due to the fact that the opacity in this case extended not only to the corneal epithelium but also to the corneal stroma.

After 14 months of continuous atovaquone administration, opacity was observed in the corneal stroma in both eyes. A similar case reported in the literature showed that opacity was present only in the corneal epithelium in both eyes after 1 month of atovaquone usage.[3] This suggests that the longer atovaquone is administered, the more the opacity extends throughout the layers of the cornea.

The use of atovaquone is not very frequent, with an average of about 1–3 patients per year administered this drug in our Rheumatology and Immunology Department. Therefore, encountering patients who have

corneal opacity during atovaquone therapy is not likely to be all that common.

In cases of atovaquone therapy where other causes of corneal opacity are unlikely, it is important to discontinue atovaquone therapy and carefully examine the patient when subjective symptoms appear, as occurred in the present case.

4. Conclusion

We encountered a rare case of bilateral corneal opacity that resulted from oral atovaquone administration. Our findings suggest that regular long-term ophthalmological examinations are necessary for patients who are taking atovaquone.

CRediT authorship contribution statement

Masafumi Uematsu: Writing – review & editing, Supervision, Project administration, Methodology. **Mohamed Talaat Mohamed:** Writing – review & editing, Resources, Investigation, Data curation. **Mao Kusano:** Writing – review & editing, Validation, Methodology. **Mohamed Yasser Helmy:** Software, Funding acquisition. **Daisuke Inoue:** Formal analysis, Data curation. **Takashi Kitaoka:** Writing – original draft, Visualization, Investigation, Conceptualization, Supervision, Project administration.

Patient consent

The patient consented to the publication of this case in writing.

Ethics Committee of Nagasaki University Hospital Approval Number: 23112028.

Authorship:

All authors attest that they meet the current ICMJE criteria for authorship.

Funding

This research received no external funding.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the patient for the participation in this study.

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