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Case report

Short-term, high-dose hydroxychloroquine corneal toxicity

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ABSTRACT

Purpose: To describe the corneal findings and management of a 61-year-old female with vortex keratopathy following short term, high dose hydroxychloroquine used in the setting of a clinical trial for recurrent breast cancer.

Observations: The patient was found to have significant corneal vortex keratopathy without retinal pathology within 3 months of 1200 mg daily hydroxychloroquine treatment as an adjuvant medication for cancer therapy. Cessation of the medication led to the resolution of the corneal verticillata within 1 month yet the vision did not return to baseline. Ultimately, remaining irregular astigmatism and ocular surface disease required a scleral contact lens to achieve a BSCVA of 20/25 OU.

Conclusions and Importance: Hydroxychloroquine-induced vortex keratopathy is largely considered dose and duration dependent and is uncommon with most standard treatment algorithms. However, with increasing use of high-dose hydroxychloroquine in adjunct cancer therapy, corneal findings are likely to become more frequent. Persistent visual impairment may occur, thus increased understanding of this pathology can aid in counseling patients and guiding treatment recommendations.

1. Introduction

Hydroxychloroquine (Plaquenil) is an aminoquinoline that is commonly used to treat malaria and a variety of rheumatic and dermatologic diseases, including systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, and porphyria cutanea tarda.[1,2] In addition to its immunomodulatory effects, hydroxychloroquine has been noted to inhibit cellular autophagy. Recently, this property of hydroxychloroquine has been exploited in the treatment of a variety of cancers to augment the effects of chemotherapy and radiation.[3] A number of phase I and phase I/II clinical trials investigating the efficacy of hydroxychloroquine drug combinations as adjuvant therapy have now been completed, with more currently underway.[3,4]

Hydroxychloroquine is generally well-tolerated, but has been associated with ocular adverse effects that are dose and duration dependent including corneal verticillata and vision threatening retinal toxicity.[1,5] As such, the American Academy of Ophthalmology (AAO) guidelines suggest a maximum daily dosage of 5.0 mg/kg real weight; at these levels the risk of retinopathy is < 1% in 5 years and less than 2% at 10 years.[5] However, an increasing number of clinical trials investigating hydroxychloroquine efficacy in cancer treatment often use doses as high as 1200 mg/day (three times greater than a typical dose) and yet little is currently known regarding potential ophthalmic consequences.[3] While corneal manifestations are generally thought to be self-limiting, herein, we report a case of significant corneal disease with subsequent visually significant alterations in corneal topography in the context of a clinical trial for recurrent breast cancer.

2. Case report

A 61-year-old, Caucasian woman with a history of Stage IIIA invasive lobular carcinoma of the left breast was referred to our service with complaints of blurred and hazy vision for approximately 1–2 months. Ophthalmic history, as noted by the referring ophthalmologist, was significant for glaucoma and bilateral dry eye but with clear corneas and a baseline vision of 20/20 OU. The patient had no known liver or renal disease and was not taking tamoxifen. Five months prior, the patient was enrolled in a phase II clinical trial to receive 600 mg twice-daily hydroxychloroquine and 10 mg once-daily everolimus, a macrolide immunosuppressant and antineoplastic agent.

On initial ophthalmic examination, best spectacle corrected visual acuity (BSCVA) was 20/70 in the right eye and 20/60 in the left eye. Intraocular pressures as measured by tonometry were 18 mmHg in both eyes. Pupillary examination, visual fields, and motility were all within normal limits. The external ocular exam was normal with the exception of mild ptosis bilaterally. The corneal exam was notable for dense, sub-

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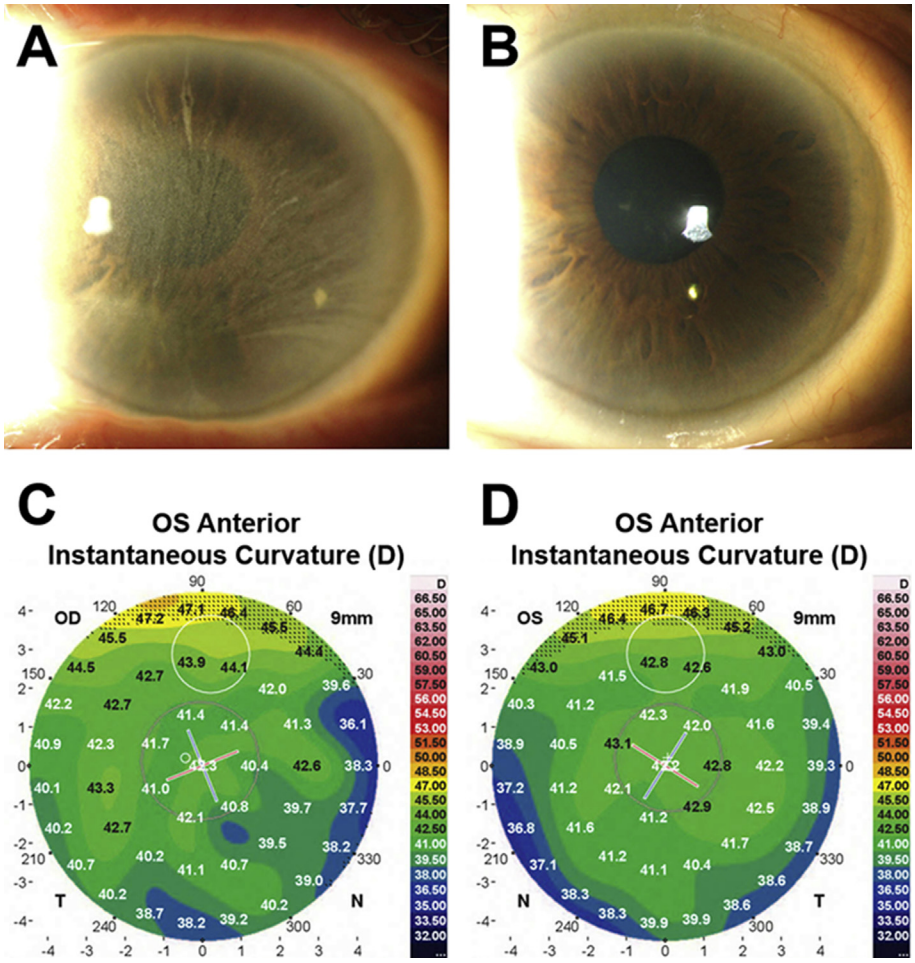

Fig. 1. Slit-lamp photography of the patient's left cornea, and topography data of the patient's corneas 5 months after stopping hydroxychloroquine treatment. A, Significant corneal verticillata after 3 months of high dose hydroxychloroquine treatment. B, Following cessation of the drug, the corneal findings completely resolved within 1 month. C, The anterior instantaneous curvature of the right cornea. D, The anterior instantaneous curvature of the left cornea. Irregular astigmatism was noted to persist in both eyes even after the cessation of the hydroxychloroquine treatment.

epithelial opacities in a whorl-like pattern with equal severity in both eyes (Fig. 1A). Mild inferior punctate epithelial erosions were also present bilaterally. Although retinal toxicity can be difficult to diagnose, a dilated fundus examination was normal with no evidence of a "bull's eye" maculopathy in either eye. Spectral-domain optical coherence tomography (OCT) imaging of the macula and a Humphrey 10–2 visual field test were also normal and did not indicate concomitant retinal disease. Given the potential systemic benefit of treatment and the absence of retinal toxicity, she continued on hydroxychloroquine with close ophthalmologic follow up.

Approximately 6 months after taking high-dose (1200mg, 21.9 mg/kg/day) hydroxychloroquine, the patient was given a drug holiday. Two weeks after drug discontinuation, corneal verticillata with inferior punctate epithelial erosions were still present, however, her BVCA vision improved to 20/40 OU. At 1 month following cessation of hydroxychloroquine, the corneal verticillata had completely resolved (Fig. 1B) yet of note, the vision remained 20/40. A complete ophthalmologic work up was done to rule out any other etiology of this persistent decreased vision including a macular OCT, retinal evaluation and neuro-ophthalmologic evaluation, all of which were unrevealing. Interestingly, the only positive finding was corneal topography that demonstrated significant irregular astigmatism (Fig. 1C and D). Despite maximum medical ocular surface management, the patient ultimately required a scleral lens to achieve a BSCVA of 20/25.

3. Discussion

The pathogenesis underlying hydroxychloroquine-induced vortex keratopathy is not completely understood, but is generally accepted to involve intra-lysosomal accumulation of lipids in the corneal epithelium either through the inhibition of lysosomal phospholipases or the formation of drug-lipid complexes.[2,6,7] As a result, the intra-lysosomal lipid-bearing inclusion bodies accumulate in the basal layers of the corneal epithelium to form a whorl-like pattern of corneal deposits.[8]

The incidence of corneal hydroxychloroquine deposits depends on both the dose and duration of drug use.[2,9] Shearer and Dubois[10] reported an incidence of corneal verticillata in patients taking 800 mg/day to be 6% within 6 months, 32% by 12 months, and 100% by 48 months with corneal findings noted as early as 2–3 weeks after starting hydroxychloroquine. In contrast, the incidence of vortex keratopathy has been reported to be 0–5% in patients taking only 400 mg/day of hydroxychloroquine.[11–13] With increasing numbers of oncologic clinical trials utilizing high doses of hyroxychloroquine, the incidence may rise significantly.

Hydroxychloroquine corneal keratopathy has been considered a relatively benign condition that resolves with drug discontinuation and typically leaves no residual corneal injury.[1,2] However, verticillata can cause visual disturbances such as halos and blurred vision from light scattering.[2,14] In the present case, while the corneal findings resolved with discontinuation of treatment, there were lingering visual symptoms, with no other ocular findings other than irregular astigmatism. To

the best knowledge of the authors, irregular astigmatism has not been reported as a sequela of corneal verticillata. While this may be attributed to the patient's long-standing diagnosis of dry eye, it is worth noting that the BSCVA prior to starting hydroxychloroquine was 20/20 OU. Ultimately the patient required a scleral contact lens to improve vision.

Importantly, while vortex keratopathy had historically not been thought to be correlated with retinal toxicity,[15] a 2003 study by Neubauer et al. challenged this common understanding and suggested that marked vortex keratopathy is associated with advanced retinopathy with 50% sensitivity and 90% specificity.[16] Given this correlation and the steady increase in active clinical trials investigating hydroxychloroquine as an adjuvant cancer therapy at doses ranging from 200 to 1200 mg/day,[4] corneal verticillata may become an important clinical finding in identifying patients with concurrent retinal disease.

4. Conclusion

As hydroxychloroquine has expanded clinical applications, corneal vortex keratopathy may become an increasingly common finding. While this report describes outcomes of a single patient, the clinical course presented here raises questions regarding hydroxychloroquine and corneal toxicity. Widely accepted dosing standards and safety assumptions may not be applicable in cases of such short-term, high-dose treatments. As such, it will be important to monitor these patients closely for retinal toxicity as well as potential lasting effects to the cornea.

Patient consent

The patient consented to publication of the case orally.

Declaration of competing interest

The authors have no relevant financial conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ajoc.2020.100713.

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Authorship

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

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