Hydroxychloroquine toxicity unmasking an occult retinitis pigmentosa carrier

The symptoms and signs of hydroxychloroquine (HCQ) retinopathy can mimic retinitis pigmentosa (RP) and both present with painless, progressive bilateral visual loss and clinical, optical coherence tomography (OCT), and electrophysiologic evidence for retinal dysfunction. We report a case of HCQ use unmasking an occult RP carrier of 2 known associated mutations. This unique presentation emphasizes the importance of consideration for genetic predisposition in atypical cases of HCQ toxicity.

A 67-year-old black female had painless progressive bilateral visual loss and night blindness for 1 year. She had systemic lupus erythematosus (SLE), prediabetes, hypertension, hyperlipidemia, and osteoporosis. Past ocular history was significant for cataract extraction in both eyes. She had prior hand surgery. Her family history was negative for glaucoma or RP. She had been treated for SLE with HCQ (Plaquenil, Concordia Pharmaceuticals Inc. St. Michael, Barbados BB11005) at a dose of 400 mg daily (approximately 5.8 mg/kg daily) for 13 years, producing a cumulative dose of 1899 g.

Serial outside ocular examinations including automated perimetry with Humphrey visual field (HVF) testing and OCT were normal, including testing 2 years prior to presentation to the neuro-ophthalmology service at Houston Methodist Hospital. At the time of the visual loss, the HCQ was discontinued, and the patient was switched to azathioprine for her SLE management. Her other medications included atenolol, gabapentin, losartan, potassium, and meloxicam.

Neuro-ophthalmic examination 10 months after discontinuation of the HCQ showed visual acuity of 20/20 bilaterally, there was no relative afferent pupillary defect, colour plates were 14/14 bilaterally, and slit-lamp examination of the anterior chamber was normal bilaterally. Intraocular pressure was 14 mm Hg OD and 12 mm Hg OS, with cup-to-disc ratios of 0.5 OD and 0.4 OS. Fundus examination was significant for moderate arteriolar attenuation and bone spicule–like pigmentation of the peripheral retinas OU (Fig. 1A; see also Supplementary Fig. 1, available online). HVF testing showed markedly decreased peripheral visual fields to central islands OU (Fig. 1C; see also Supplementary Fig. 1, available online). OCT optic nerve global retinal nerve fibre layer thickness was 76 μm OD and 75 μm OS. Macular OCT showed ellipsoid zone disruption (not present on OCT performed 3 years prior) consistent with HCQ toxicity (Fig. 1B; see also Supplementary Fig. 1, available online).

Laboratory studies including erythrocyte sedimentation rate, C-reactive protein, interferon gamma release assay for tuberculosis, paraneoplastic antibody, syphilis serology, and chest x-ray were negative. The patient's creatinine was elevated at 1.11 mg/dL with a low estimated glomerular filtration rate of 52 mL/min/1.73 m^2.

Computed tomography and magnetic resonance imaging of the brain were normal. Full-field electroretinogram (ERG) tracings showed essentially extinguished scotopic and photopic responses and revealed diffuse functional impairment of peripheral photoreceptors (rods and cones) and inner nuclear layers (bipolar cells and Mueller cells) OU (Fig. 1D; see also Supplementary Fig. 1, available online).

Genetic testing panel for RP showed heterozygosity in the *CRB1* gene for the sequence variant designated c.2506C>A. This gene has been reported in patients with autosomal recessive forms of RP.[1] The patient also was found to be heterozygous at the *RDH12* gene for sequence variant c.542G>A. Known pathogenic variants in *RDH12* have been associated with autosomal recessive Leber congenital amaurosis and autosomal dominant and autosomal recessive RP.[2] At the patient's last 2-year follow-up in the neuro-ophthalmology clinic, her vision and visual field were unchanged.

RP includes a heterogeneous group of inherited retinal disorders (syndromic and nonsyndromic) that cause painless progressive visual loss due to degeneration of retinal photoreceptors. The disorder affects both rods and cones, but rod-predominant and cone-predominant forms of RP exist. Typical symptoms of RP include peripheral visual field loss and night blindness OU, and characteristic fundus findings develop over time (e.g., retinal arteriolar narrowing, bone

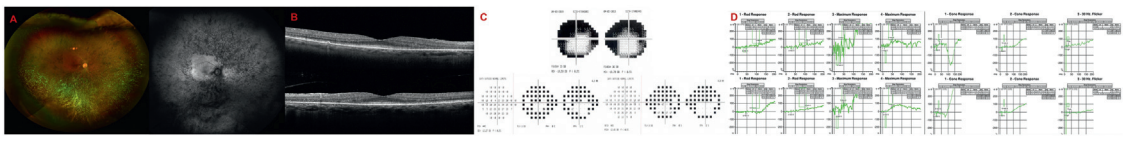

Fig. 1—(A) Wide-field colour and infrared OD fundus photographs depicting diffuse retinal pigmental epithelium changes with bone spicules. View partly obscured by asteroid hyalosis. OS photographs excluded because of obscured view secondary to posterior capsular opacification. (B) Optical coherence tomography of the macula showing ellipsoid zone disruption bilaterally (top picture OD and bottom picture OS). (C) Humphrey visual field 24-2 showing superior and inferior arcuate defect bilaterally. (D) Full-field electroretinogram showing both scotopic and photopic responses essentially extinguished OU.

https://doi.org/10.1016/j.jcjo.2023.01.014
ISSN 0008-4182

Table 1—Reported cases of hydroxychloroquine toxicity in patients with retinitis pigmentosa

Case	Study	Year	Patient details	Duration of HCQ use, y	Cumulative dose of HCQ, g	Ocular signs and symptoms at presentation	Clinical indication for HCQ use	RP-associated genetic mutation(s) identified
1	Marmor et al.[4]	2016	Unknown	Unknown	Unknown	Unknown	Unknown	Genetic testing not performed
2	Katsman et al.[6]	2017	39-year-old female	20	2774 (400 mg/kg/d)	Decreased VA, nyctalopia, peripheral vision loss	SLE	*USH2A* gene heterozygous mutation
3	Patel et al.[7]	2021	74-year-old female	2.5	132.5 (200 mg/d)	Nyctalopia, pericentral vision loss	RA	*HGSNAT* gene homozygous missense variant c.1843G>A
4	This study	2022	67-year-old female	13	1899 (400 mg/kg/d)	Nyctalopia, peripheral vision loss	SLE	*CRB1* gene heterozygous for sequence variant c.2506C>A; *RDH12* gene heterozygous for sequence variant c.542G>A

HCQ, hydroxychloroquine; RP, retinitis pigmentosa; VA, visual acuity; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.

spicule formation), but retinal abnormalities may be subtle in some cases (RP sine pigmento). Pericentral forms of RP can produce paracentral rather than peripheral visual field loss OU. Autosomal dominant, autosomal recessive, and X-linked inheritance patterns occur in RP.

This patient had 2 predisposing genetic mutations associated with RP and was previously asymptomatic and had normal ocular examinations prior to and even during initial treatment with HCQ. She had several risk factors for HCQ toxicity, however, including duration (>5 years of use), daily dosing (>5 mg/kg daily dosing per absolute body weight), compromised renal function,[3] and cumulative dose (threshold >1000 g). The typical ring scotoma of HVF loss in this case, however, was associated with retinal pigment epithelial change and bone spicule formation, which is not a feature of typical HCQ toxicity, which characteristically produces a "bull's eye" maculopathy.

There are prior cases of severe HCQ toxicity mimicking RP with more typical diffuse retinal degeneration and reduced full-field ERG, suggesting that retinal dystrophy may predispose to HCQ toxicity.[4] Both late-stage HCQ toxicity and late-stage RP may show diminished scotopic and photopic responses on ERG. ERG alone, however, will not differentiate between late HCQ toxicity and RP. In such cases, we recommend genetic testing for RP. Interestingly, ongoing clinical trials are investigating HCQ as a proposed treatment for an autosomal dominant form of RP.[5] We reviewed the PubMed and Google Scholar databases and identified 3 other cases of HCQ toxicity observed in patients with RP (Table 1; see also Supplementary Table 1, available online). Our patient's case of HCQ toxicity unmasking an occult autosomal recessive carrier state of RP is unique in the literature because of the presence of 2 known associated mutations that are presumed to be de novo given the patient's negative family history. Current guidelines for HCQ screening define prior macular disease as a risk factor for toxicity, and although RP is not explicitly listed as a risk factor, patients with unusual peripheral visual field loss or night blindness symptoms should be evaluated for underlying retinopathy.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2023.01.014.

Pranati Ahuja,[a] Ardalan Sharifi,[a] Mohammad Pakravan,[b] Amy C. Schefler,[b,g] Andrew G. Lee[a,b,c,d,e,f]

[a]University of Texas Medical Branch, Galveston, TX; [b]Blanton Eye Institute, Houston Methodist Hospital, Houston, TX; [c]Weill Cornell Medicine, New York, NY; [d]University of Texas MD Anderson Cancer Center, Houston, TX; [e]Texas A and M College of Medicine, Bryan, TX; [f]University of Iowa Hospitals and Clinics, Iowa City, IA; [g]Retina Consultants of Texas, Houston, TX.

Originally received Aug. 12, 2022. Final revision Nov. 28, 2022. Accepted Jan. 22, 2023.

Correspondence to Andrew G. Lee, MD; aglee@houstonmethodist.org.

References

1. Bujakowska K, Audo I, Mohand-Saïd S, et al. *CRB1* mutations in inherited retinal dystrophies. Hum Mutat 2012;33:306–15.
2. Mackay DS, Dev Borman A, Moradi P, et al. *RDH12* retinopathy: novel mutations and phenotypic description. Mol Vis 2011;17:2706–16.
3. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. American Academy of Ophthalmology recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 Revision). Ophthalmology. 2016;123:1386–94.
4. Marmor M. Retinitis pigmentosa or severe hydroychloroquine retinopathy? Invest Ophthalmol Vis Sci 2016;57:157.
5. Oral hydroxychloroquine (HCQ) for retinitis pigmentosa caused by P23H- rhodopsin (RHO) [Internet]. ClinicalTrials.gov identifier: NCT04120883. Updated February 15, 2022.

Available at: https://clinicaltrials.gov/ct2/show/NCT04120883 (accessed February 24, 2022).

6. Katsman D, Sanfilippo C, Sarraf D. Panretinal degeneration associated with long-term hydroxychloroquine use and heterozygous *USH2A* mutation. Retin Cases Brief Rep 2017;11 (Suppl 1):S77–80.
7. Patel P, Jones K, Friedman DI, Birch DG, Ufret-Vincenty RL. Unexpected etiology in a case of bilateral maculopathy. Case Rep Ophthalmol 2021;12:622–8.

Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this correspondence.