

When annual screening is lost in long-term hydroxychloroquine users: Three illustrative cases

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ABSTRACT

Purpose: To illustrate the clinical consequences of prolonged loss to follow-up for annual screening in long-term hydroxychloroquine users through representative cases of hydroxychloroquine retinopathy.

Observations: Three Korean women with systemic lupus erythematosus who had received hydroxychloroquine 200 mg daily for 12–20 years were evaluated after being lost to recommended annual retinal screening for 4–6 years. All patients showed pericentral retinopathy but were asymptomatic. Fundus autofluorescence demonstrated pericentral abnormalities ranging from localized temporal hyperautofluorescence to extensive pericentral hypoautofluorescence. Despite prompt discontinuation of hydroxychloroquine, follow-up imaging showed progression with expansion of abnormal pericentral autofluorescence in all cases.

Conclusions and importance: These cases highlight that interruption of annual screening in long-term hydroxychloroquine users may allow silent progression to advanced retinopathy, which can continue despite cessation of therapy. The findings underscore the critical importance of sustained adherence to screening recommendations, particularly in patients with risk factors.

1. Case report

Three Korean women with systemic lupus erythematosus (ages 36, 69, and 61 years; body weights 40, 49, and 40 kg, respectively) were treated with hydroxychloroquine at a daily dose of 200 mg for 14 (Case A, Fig. 1), 12 (Case B, Fig. 2), and 25 (Case C, Fig. 3) years. All patients had previously adhered to recommended annual screening, with normal findings at their last examinations. Two patients missed their scheduled annual screening visits and were subsequently lost to follow-up, whereas one patient transferred care after relocating but did not undergo ophthalmic screening thereafter. Following referral by their rheumatologists (prescribing physicians) for hydroxychloroquine screening, they returned for ophthalmic evaluation after gaps of 4, 5, and 6 years, respectively. Tamoxifen use, a recognized risk factor for hydroxychloroquine retinopathy,^{1,2} was absent in all patients. Renal disease, another established risk factor, was present in one patient (Case A). Upon return for screening after a prolonged lapse in follow-up, all patients were asymptomatic. The best-corrected visual acuity of the eye shown in each figure was 20/20, 20/25, and 20/25 for Cases A, B, and C, respectively. Fundus autofluorescence imaging (Figs. 1–3, top) revealed

hydroxychloroquine retinopathy in all three cases, characterized by pericentral abnormalities ranging from localized temporal hyperautofluorescence (Fig. 1) to more extensive pericentral hyperautofluorescence or hypoautofluorescence (Figs. 2 and 3, white arrows). Corresponding optical coherence tomography (OCT) images (Figs. 1–3, bottom) demonstrated matching pericentral ellipsoid zone disruption in all three cases at the time of return. Hydroxychloroquine was discontinued immediately in all patients. Follow-up fundus autofluorescence imaging obtained one year later demonstrated progression, with expansion and increased conspicuity of the abnormal pericentral autofluorescence (yellow arrows). Corresponding OCT images also showed further progression of ellipsoid zone loss despite drug cessation.

2. Discussion

These cases illustrate that interruption of recommended annual screening may permit silent progression of hydroxychloroquine retinopathy in long-term users. Although long-term follow-up of hydroxychloroquine retinopathy has been reported previously, the literature remains limited regarding the development and progression of

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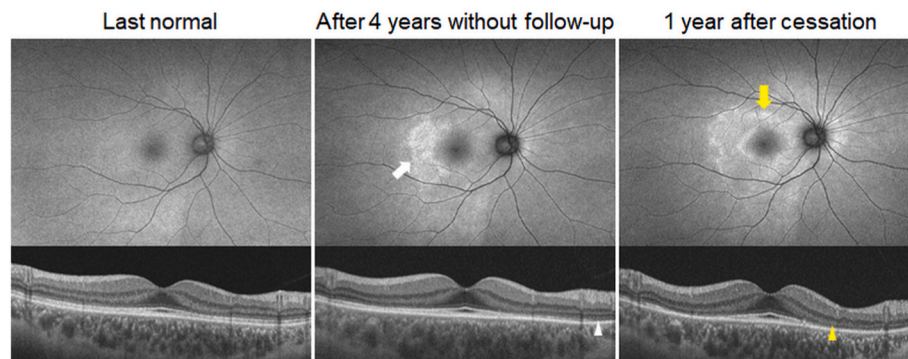


Fig. 1. Case A. Fundus autofluorescence (FAF; top) and corresponding optical coherence tomography (OCT; bottom) obtained at the last normal screening, after 4 years without follow-up, and 1 year after hydroxychloroquine discontinuation. At return after the follow-up lapse, pericentral hyperautofluorescence and ellipsoid zone loss were observed, indicated by the white arrow and arrowhead, respectively. One year after hydroxychloroquine discontinuation, progression with enlargement of the hyperautofluorescence (yellow arrow) and ellipsoid zone loss (yellow arrowhead) is demonstrated. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

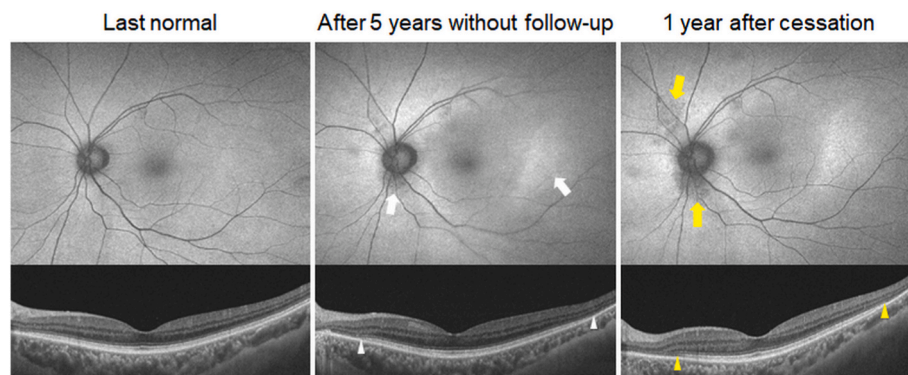


Fig. 2. Case B. Fundus autofluorescence (FAF; top) and corresponding optical coherence tomography (OCT; bottom) obtained at the last normal screening, after 5 years without follow-up, and 1 year after hydroxychloroquine discontinuation. At return after the follow-up lapse, pericentral hyperautofluorescence, peripapillary hypoautofluorescence, and ellipsoid zone loss were observed, indicated by the white arrows or arrowheads. One year after hydroxychloroquine discontinuation, progression with enlargement of the hypoautofluorescence (yellow arrows) and ellipsoid zone loss (yellow arrowheads) is demonstrated. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

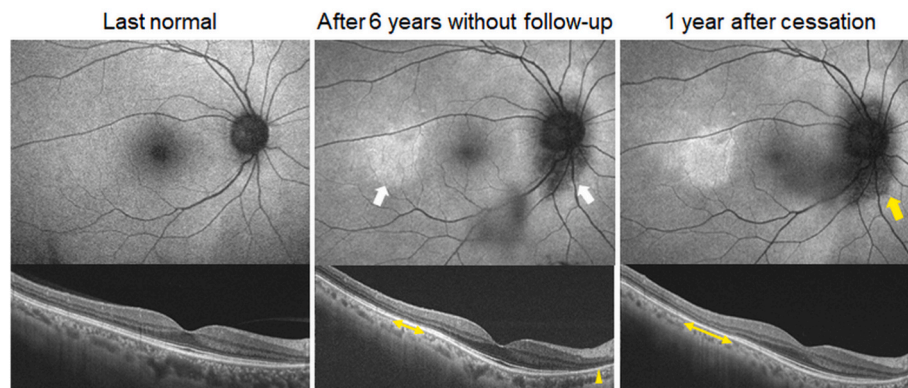


Fig. 3. Case C. Fundus autofluorescence (FAF; top) and corresponding optical coherence tomography (OCT; bottom) obtained at the last normal screening, after 6 years without follow-up, and 1 year after hydroxychloroquine discontinuation. At return after the follow-up lapse, peripapillary hypoautofluorescence (white arrows) and pericentral ellipsoid zone loss (yellow arrowhead and double arrow) were observed. One year after hydroxychloroquine discontinuation, progression with enlargement of the hypoautofluorescence (yellow arrow) and ellipsoid zone loss (double arrow) is demonstrated. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

retinopathy after a prolonged lapse in recommended annual screening among long-term hydroxychloroquine users. Treatment duration is one of the key risk factors, and lower body weight may further increase susceptibility because the commonly prescribed daily dose (200 mg or

400 mg) results in relatively higher mg/kg exposure in smaller individuals. According to the American Academy of Ophthalmology recommendations, a maximum daily dose of ≤ 5.0 mg/kg based on actual body weight is advised.^{1,2} The estimated daily doses in cases A–C were

approximately 5.0, 4.1, and 5.0 mg/kg/day, respectively, highlighting that hydroxychloroquine retinopathy may occur despite dosing within the currently recommended range. Importantly, hydroxychloroquine retinopathy may remain asymptomatic despite detectable retinal damages, and disease progression can continue even after discontinuation of the medication.³ The mechanism underlying continued progression of hydroxychloroquine retinopathy after drug discontinuation remains incompletely understood. One possible explanation is that hydroxychloroquine accumulates within retinal pigment epithelial lysosomes, where its prolonged intracellular retention can cause persistent lysosomal dysfunction and impaired autophagy, leading to further outer retinal degeneration. In addition, RPE damage already present before drug cessation may become clinically more apparent over time, giving the appearance of continued disease progression. However, this hypothesis remains speculative, and further studies are needed to clarify the underlying pathophysiology. These observations emphasize the importance of annual screening in long-term users.^{1,2}

3. Conclusions

Loss of annual screening in long-term hydroxychloroquine users can lead to unrecognized progression of hydroxychloroquine retinopathy that may continue despite cessation of therapy. Continuous adherence to annual screening protocols is therefore essential, particularly in patients with prolonged treatment duration and relatively low body weight.

Patient consent

Written informed consent for publication of the case details and accompanying images was not obtained because the patients are no longer under clinical follow-up. All data were fully anonymized so that individuals cannot be identified. The Institutional Review Board of Hanyang University Hospital reviewed the protocol and granted a waiver of written informed consent (IRB waiver/approval no.: 2025-06-049). All procedures were conducted in accordance with the Declaration of Helsinki and applicable local regulations.

Authorship

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Moonsu Kim: Data curation, Investigation, Methodology, Resources, Visualization, Writing – original draft. **Seong Joon Ahn:** Conceptualization, Data curation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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.

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