



# Macular Toxicity after Long-Term Hydroxychloroquine Therapy- A Case Series

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## KEYWORDS

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## ABSTRACT:

Hydroxychloroquine is widely prescribed across multiple medical specialties for the long-term management of autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis.<sup>1</sup> Although considered safer than chloroquine, prolonged use of hydroxychloroquine carries the risk of irreversible macular toxicity, which can lead to permanent vision impairment.<sup>2,3</sup> Several factors may elevate the risk of developing retinal toxicity from hydroxychloroquine use. These include taking more than 6.5 mg/kg per day, being obese, using the medication for over five years, having compromised kidney or liver function, being older than 60, or having an existing retinal condition.<sup>4</sup>

## Introduction

Hydroxychloroquine is widely prescribed across multiple medical specialties for the long-term management of autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis.<sup>1</sup> Although considered safer than chloroquine, prolonged use of hydroxychloroquine carries the risk of irreversible macular toxicity, which can lead to permanent vision impairment.<sup>2,3</sup> Several factors may elevate the risk of developing retinal toxicity from hydroxychloroquine use. These include taking more than 6.5 mg/kg per day, being obese, using the medication for over five years, having compromised kidney or liver function, being older than 60, or having an existing retinal condition.<sup>4</sup>

In the early stages, macular toxicity is often asymptomatic, with abnormalities detected only through fundus examination or advanced imaging techniques like optical coherence tomography (OCT). Since no effective treatment exists to reverse hydroxychloroquine-induced retinal damage, early recognition and timely discontinuation of therapy are critical in preventing further progression.<sup>5</sup> The exact mechanism of toxicity remains unclear, but evidence suggests that the drug binds to melanin within the retinal pigment epithelium (RPE), potentially leading to cumulative cellular damage over time.<sup>6</sup> HCQ maculopathy is not reversible and cellular damage may progress for a number of years even after the drug is stopped. Therefore, it is essential to continue following the patient appropriately.<sup>7</sup>

This report highlights three cases of hydroxychloroquine-induced macular toxicity in patients undergoing treatment for more than five years, emphasizing the importance of regular ophthalmic screening for early detection

## Stages of HCQ maculopathy<sup>8</sup>

**Early Stage:** In the initial phase, optical coherence tomography (OCT) may reveal subtle structural changes, including parafoveal thinning and a diminished or absent foveal depression. Disruption or loss of the ellipsoid zone (EZ) can also be an early indicator of toxicity.

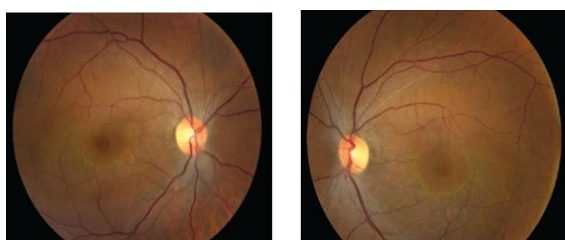
**Intermediate Stage:** As toxicity advances, the damage extends beyond the parafoveal region, with progressive thinning and further disorganization of the EZ. The interdigitation zone (IZ) may also be affected, showing signs of disruption. Additionally, increased reflectivity and irregularities in the retinal pigment epithelium (RPE) layer may become more apparent.

**Advanced Stage:** In severe cases, extensive damage to both the EZ and IZ occurs across the macula. A characteristic "flying saucer" appearance may develop, where the central foveal region remains relatively intact while the surrounding outer retinal layers become significantly thinned or completely absent, creating a saucer-like depression. In advanced stages, marked RPE atrophy, along with the degeneration of the outer nuclear layer (ONL) and inner retinal layers, can be observed, leading to significant visual impairment.

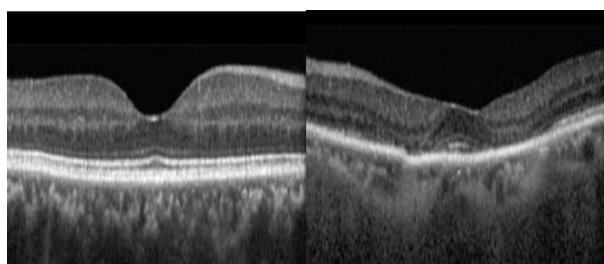


### Case scenario 1

A 50-year-old woman, undergoing treatment for rheumatoid arthritis with hydroxychloroquine for the past six years, presented for a routine ophthalmic evaluation. On examination, her visual acuity was 6/9 in both eyes (near improvement with pinhole), with normal colour vision. Fundus examination revealed characteristic bull's eye maculopathy in the perifoveal region of both eyes, figure 1. Further imaging with spectral-domain optical coherence tomography showed a distinctive "flying saucer" sign, indicative of advanced macular toxicity, figure 2.



**Figure 1 Fundus examination showing bull's eye maculopathy**

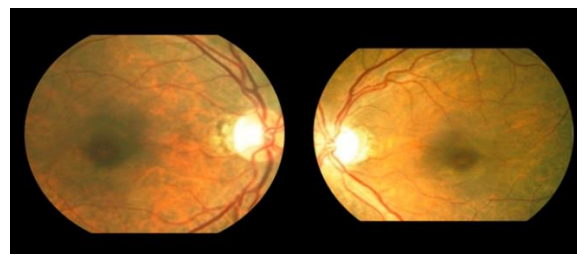


**Figure 2 Spectral-domain Optical Coherence Tomography (OCT) with "flying saucer" sign**

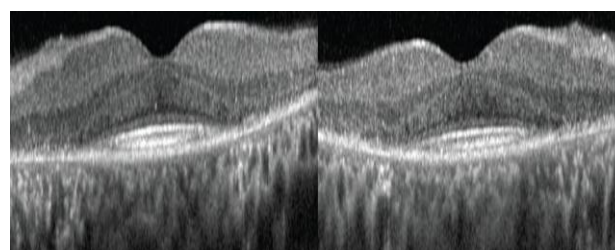
### Case scenario 2

A 61-year-old male, diagnosed with rheumatoid arthritis and on hydroxychloroquine therapy for six years, presented with progressive vision loss in both eyes over the past eight months. He also has a history of hypertension for three years. On examination, visual acuity in the right eye was 6/12, improving to 6/9 with pinhole correction, while the left eye had a visual acuity of 6/18 (near improvement with pinhole). Colour vision remained normal in both eyes. Fundus evaluation revealed areas of hypopigmentation superior, inferior, and temporal to the macula in both eyes, figure 3. Spectral-domain optical coherence tomography showed the characteristic "flying saucer" sign along with

thinning of the external limiting membrane and the outer nuclear layer, suggestive of hydroxychloroquine-induced macular toxicity, figure 4.



**Figure 3 Fundus examination showing bull's eye maculopathy**



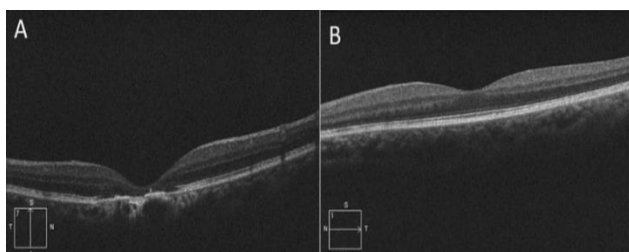
**Figure 4 Spectral-domain Optical Coherence Tomography (OCT) with "flying saucer" sign, thinning of the external limiting membrane and the outer nuclear layer**

### Case scenario 3

A 63-year-old female, diagnosed with rheumatoid arthritis for a decade and on hydroxychloroquine therapy for the past eight years, presented with progressive blurring of vision for one year, which was more pronounced in the right eye than the left. She had no other known comorbidities or concurrent medications. On examination, her visual acuity was 6/60 in the right eye with no improvement and 6/12 in the left eye, improving to 6/9 with pinhole correction. Colour vision testing revealed red-green deficiency in the right eye, while the left eye remained normal. Fundus examination showed an annular zone of depigmentation in the macular region of the right eye, while the left eye appeared normal, figure 5. Spectral-domain optical coherence tomography revealed retinal pigment epithelium thinning in the right eye, with no abnormalities detected in the left, figure 6. Findings were suggestive of hydroxychloroquine-induced macular toxicity.



**Figure 5 Fundus examination showing annular zone of depigmentation in right eye**



**Figure 6 Spectral-domain Optical Coherence Tomography (OCT) with retinal pigment epithelium thinning in the right eye**

## Discussion

Hydroxychloroquine (HCQ) retinopathy is a rare but potentially irreversible adverse effect associated with long-term HCQ therapy. This case series presents three patients diagnosed with HCQ-induced retinal toxicity, highlighting risk factors, clinical presentations, and imaging findings. A comparative analysis with existing literature provides insight into disease progression, risk stratification, and management strategies.

## Comparison with Existing Studies

Our case series observed HCQ retinopathy in patients treated for 5 to 15 years, with cumulative doses ranging from 1000 g to 2000 g. These findings align with Melles et al. who reported increased toxicity risk beyond 1000 g.<sup>9</sup> Similarly, Wolfe and Marmor identified HCQ use exceeding five years as a critical risk factor, reinforcing the importance of periodic screening.<sup>10</sup>

A study by Yusuf et al. have emphasized risk factors such as renal impairment and obesity.<sup>1</sup> In our series, two patients had comorbid conditions, including diabetes and renal dysfunction, likely contributing to retinal toxicity. Rao et al. similarly reported a higher toxicity rate in patients with renal impairment due to reduced drug clearance, underscoring the need for dose adjustments in at-risk individuals.<sup>11</sup>

The spectrum of symptoms in our case series ranged from subtle paracentral scotomas to significant central vision loss. Early symptoms are often nonspecific and only detectable through screening tests.<sup>6</sup> Annual screening should be considered if high dose or long term treatment is required.<sup>7</sup> One of our cases involved an asymptomatic patient diagnosed during routine screening, highlighting the importance of baseline examination and regular ophthalmologic evaluations, as recommended by AAO guidelines (2021).<sup>12</sup>

Optical coherence tomography (OCT) and fundus autofluorescence (FAF) were instrumental in diagnosing HCQ toxicity, revealing parafoveal atrophy and perifoveal hyperautofluorescence. Marmor et al. and Pandey et al. corroborate these findings, emphasizing the sensitivity of spectral-domain OCT in detecting early structural changes before functional deficits manifest.<sup>13,14</sup>

The irreversible nature of HCQ-induced retinal toxicity underscores the need for early detection. HCQ discontinuation was the primary management strategy in our cases, consistent with recommendations from Ahn et al. (2019).<sup>15</sup> However, one patient experienced progressive visual decline post-discontinuation, a phenomenon described by Lee et al., where retinal atrophy continued despite cessation of therapy.<sup>16</sup>

## Conclusion

This case series reinforces the necessity of individualized risk assessment and adherence to screening guidelines for HCQ-induced retinal toxicity. Comparative analysis with previous studies underscores the importance of multimodal imaging and risk stratification based on cumulative dose, treatment duration, and patient-specific factors. Future research should focus on refining screening protocols and exploring neuroprotective strategies to mitigate retinal damage in high-risk individuals.

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