Non-leaking cystoid macular edema and bull’s eye maculopathy caused by hydroxychloroquine toxicity in Asian patients

Low Kah Ling, Nor Azita Ahmad Tarmidzi, Hamisah Ishak, Jamalia Rahmat, Jemaima Che Hamzah

ABSTRACT

Introduction: Hydroxychloroquine (HCQ) is used for treating systemic lupus erythematosus (SLE). It can cause irreversible toxic retinopathy, we discuss the outcome of HCQ retinopathy and emphasize the distinct toxicity pattern in Asian patients.

Case Series: We report a retrospective case series of two systemic lupus erythematosus (SLE) patients who presented with HCQ toxicity. Both Asian SLE patients were treated with HCQ over five years with cumulative dose of >1000 g. Both had characteristic findings on spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF). First patient had non-leaking cystoid macula edema (CME) associated with HCQ retinopathy and second patient had bull’s eye maculopathy (BEM). They exhibited different outcome after drug cessation. There was no disease progression in former whereas latter lost her central vision over two years.

Conclusion: Non-leaking CME is rare and can be a sequence of HCQ retinopathy. Bull’s eye maculopathy is another manifestation of severe HCQ toxicity. Toxic damage to retina is irreversible, and may progress even after the drug is stopped, so is crucial to discontinue once toxicity is detected. Patients on HCQ warrant annual screening with multimodal imaging. There are racial differences in HCQ toxicity, hence distinct screening tests should be performed in Asian population.

Keywords: Cystoid macula edema, Hydroxychloroquine, Maculopathy

INTRODUCTION

Hydroxychloroquine (HCQ) is an antimalarial agent that is widely used for treating systemic lupus erythematosus (SLE) [1]. It is generally a safe drug; however, it can cause irreversible toxic retinopathy. The incidence of toxicity is about 7.5% when duration of exposure is more than five years [2]. Its toxic effects on the retina manifest as parafoveal photoreceptor loss and retinal pigment epithelium (RPE) atrophy generate an end stage bull’s eye pattern of maculopathy [3]. Other macula complications may arise in HCQ toxicity and non-leaking cystoid macular edema (CME) is uncommon [4]. We report and discuss the clinical presentation, outcome, and management in two patients with HCQ toxicity.
CASE SERIES

Case 1

A 41-year-old Malay woman with SLE was referred by her rheumatologist for bilateral blurred vision over three weeks. She had been on hydroxychloroquine daily dose of 4.4 mg/kg of real body weight (6.6 mg/kg of ideal body weight) over 13 years with cumulative dose of 1898 g. She was also on oral prednisolone and mycophenolate mofetil for her systemic sclerosis. Her SLE disease was well controlled and renal function was normal.

At presentation, her best corrected visual acuity (BCVA) reduced from baseline 6/6 to 6/18 bilaterally. Anterior segments were normal. Funduscopic examination showed dull foveal reflex in both eyes. Optic discs, vessels, and peripheral retinas were normal. No signs of inflammation noted.

Optical coherence tomography (OCT) demonstrated bilateral outer retinal atrophy in temporal macula, loss of photoreceptor layers parafoveally, and CME (Figure 1A). Fundus autofluorescence showed patchy hyperautofluorescence and parafoveal hypoautofluorescence in both eyes (Figure 1B). On the other hand, both eyes fluorescein angiography (FA) revealed central hypofluorescence without late phase leakage (Figure 1C). There was no vessels wall staining or leakage elsewhere.

Diagnosis of HCQ toxicity with non-leaking CME was made. HCQ was discontinued. Two months later, her vision improved with drug cessation. Optical coherence tomography showed reduction of foveal thickening with residual intraretinal cystic spaces (Figure 1D). Her retinal toxicity did not progress over one year as evident by BCVA and OCT.

Case 2

A 34-year-old Malay woman with SLE was referred by her nephrologist for progressive blurring of left eye vision over one month. She had been on hydroxychloroquine daily dose of 7.8 mg/kg of real body weight (8 mg/kg of ideal body weight) over nine years for a cumulative dose of 1314 g. Her renal function was impaired due to lupus nephritis. She was also on oral cyclosporin and prednisolone at the time of presentation. She denied history of ocular inflammation, trauma, or surgery. She defaulted her annual eye check for past five years.

Her BCVA was 6/9 in the right eye and 6/12 in the left eye. The anterior segments were normal. Funduscopic examination disclosed BEM bilaterally and a thin cellophane membrane on the right macula (Figure 2A).

Optical coherence tomography demonstrated flying saucer sign in the right eye and left eye showed widespread outer retina layer atrophy involving fovea (Figure 2B). Fundus autofluorescence of both eyes revealed patchy hyperautofluorescence in the macula and hypoautofluorescence in the parafoveal area (Figure 2C). Humphrey visual field (HVF) 24-2 testing demonstrated dense central visual defect extends beyond 24°, more severe in the temporal area in both eyes. This is corresponding to the widespread atrophy seen on OCT and FAF (Figure 2D).

Diagnosis of HCQ toxicity with BEM was entertained and the drug was discontinued. Her visual acuity reduced to 6/36 and 6/60 in the right and left eye respectively over two years despite drug cessation. Optical coherence tomography showed progressive loss of photoreceptor layer in both eyes and presence of right epiretinal membrane (ERM) (Figure 2E).

DISCUSSION

Hydroxychloroquine retinopathy is a disease that progresses slowly. Symptomatic visual impairment usually happened late in the disease course [5]. More recently, other retinal complications such as CME and ERM have been reported [4, 6]. Nevertheless, their prevalence is rare and can be under-detected before the emergence of modern imaging technology.
It was postulated that HCQ binds to melanin in RPE contributing to the toxic concentration on retina. This leads to dysfunction of RPE and breakdown of outer blood retinal barrier, subsequently allow fluids to accumulate in retina, with that CME developed [4, 7]. Knowledge of underlying mechanism in CME is essential to a rational therapeutic approach, hence, is it crucial to exclude other inflammatory disorders, inherited dystrophies in patients taking HCQ [11].

Hydroxychloroquine toxicity is of serious ophthalmologic concern because it is not treatable. Nonetheless, treatment of CME in HCQ retinopathy has not been formally established. Topical non-steroidal anti-inflammatory drugs (NSAIDs), intravitreal triamcinolone showed poor response [7], whereas topical or systemic carbonic anhydrase inhibitors demonstrated varying success [7–9].

Severity of toxicity is classified into mild (patchy photoreceptor loss on SD-OCT or isolated VF defect), moderate (photoreceptor damage and scotoma comprising a partial or full ring) and severe (RPE damage visible on SD-OCT or hypofluorescence on FAF) [12]. Severe HCQ toxicity can produce a characteristic “bull’s eye,” an intact foveal area surrounded by a depigmented ring of RPE atrophy on fundus examination [3]. Our patients had severe HCQ toxicity, showing BEM with changes in OCT and FAF.

Hydroxychloroquine retinopathy can progress despite drug cessation, possibly occurs at a greater tendency in severe toxicity [13]. It was hypothesized that HCQ inhibits lysosomal degradation of RPE cells result in entrapment of HCQ in the RPE therefore disease continues to progress [13]. Classically, initial toxic damage occurs at parafovea photoreceptors. If toxic exposure continues, the damage can encroach on fovea and results in permanent central vision loss [3]. Our second patient continued to lose her foveal photoreceptor, RPE and central vision in both eyes over two years even after HCQ was stopped. Thus, the goal at present is to catch toxicity early before significant functional loss.

The first and foremost goal is to identify patients who are at risk of HCQ retinopathy. The main risk factor for toxicity is daily consumption of more than 5.0 mg/kg of real weight. Risk increases exponentially with increasing dose. Other important risk factors include cumulative dose of 1000 g, concomitant renal impairment or tamoxifen therapy [3]. It is worth to notice that our patients were overdosed, and this explains the more severe toxicity and the progression. According to 2016 Recommendations Guideline of American Academy of Ophthalmology [3], all patient beginning long-term HCQ should have a baseline fundus examination within the first year of starting the drug. Annual screening can then be started five years after therapy if no major risk factors and continued annually [14]. Annual screening should include fundus examination, OCT and FAF [14]. Questionable results must be validated with additional procedures [14].
Hydroxychloroquine toxicity manifests in three patterns, parafoveal (retinal changes 2–6° from the fovea), pericentral (retinal changes ≥8° from the fovea) or mixed (retinal changes in both parafoveal and pericentral) [12]. Mixed and pericentral pattern were detected in 83% of Asians and 9% of Caucasians [12]. Our patients are Southeast Asian, and both demonstrated pericentral and parafoveal toxicity, fitting into the mixed toxicity pattern. Nonetheless, we also found that temporal area appears to be more severely affected in our patients. Consequently, ophthalmologists should perform either 24-2 or 30-2 visual fields test instead of 10-2 in Asian population to avoid overlooking early toxicity [3].

It is important to affirm that HCQ is a useful drug and has fewer systemic side effects than many of the alternative medications used for immune diseases [3]. Thus, decision of drug cessation should be made only when definite toxicity is recognized.

CONCLUSION

In conclusion, both non-leaking CME and BEM are the late manifestation of HCQ retinopathy. No treatment has yet proven effective to treat HCQ retinopathy, CME in HCQ retinopathy, and BEM other than discontinuation of drug. Daily consumption of HCQ more than 5.0 mg/kg of real weight is the main risk factor for toxicity. It can lead to more severe toxicity and disease progression. Annual screening is crucial for early recognition of disease. Multimodal imaging, including OCT and FAF, should be performed during each annual screening. Asian population is more prone to mixed pattern toxicity, therefore 24-2 or 30-2 visual field tests should be obtained when necessary.

REFERENCES


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Author Contributions

Low Kah Ling – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Nor Azita Ahmad Tarmidzi – Conception of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Hamisah Ishak – Conception of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jamalia Rahmat – Interpretation of data, Revising the work critically for important intellectual content, Final
approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jemaima Che Hamzah – Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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