Case Report

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Macular edema might be a rare presentation of hydroxychloroquine-induced retinal toxicity

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Abstract:

The aim of this study is to report a rare case of macular edema as a presentation of hydroxychloroquine-related retinal toxicity. We presented a case of a 46-year-old female patient using hydroxychloroquine for underlying rheumatoid arthritis (RA) with blurred vision over the left eye. Uveitis and macular edema were found initially. Systemic survey did not reveal any other etiology. Topical corticosteroid was given under the impression of RA-related uveitis. The uveitis resolved 1 week later, but macular edema persisted in spite of treatment. Under the suspicion of drug-related complication, we try to discontinue hydroxychloroquine. Her symptoms improved gradually after cessation of hydroxychloroquine, and further serial image study confirmed subsiding of the macular edema without any further treatment. Except the well-known signs of the retinal toxicity, macular edema might be a rare presentation of hydroxychloroquine-related retinal toxicity.

Keywords:

Hydroxychloroquine, macular edema, optical coherence tomography, retinal toxicity

Introduction

Hydroxychloroquine, frequently used in the long-term treatment of many autoimmune diseases, had been reported with retinal toxicity, including depigmentation of the paracentral retinal pigment epithelium (RPE), bull's-eye maculopathy, and even widespread retinal atrophy and visual loss.[1] However, there was seldom previous formal report of macular edema formation. We presented a case of rheumatoid arthritis (RA) under hydroxychloroquine, who initially presented as uveitis and macular edema. Based on the clinical course, macular edema was considered to be a presentation of hydroxychloroquine-related retinal toxicity.

Case Report

A 46-year-old female patient (161.0 cm in height and 58.0 kg in weight) presented at the clinic with complaints of blurred vision in her left eye for several months. She had a history of RA under regular treatment for about 3 years of oral hydroxychloroquine (dosage: 400 mg/day irregularly for 18 months, accumulative dose: 145.6 g), sulfasalazine, methotrexate, prednisolone, and etanercept with fluctuated disease control. At the time of presenting, she was under sulfasalazine, methotrexate, prednisolone, and hydroxychloroquine.

Examination showed best-corrected visual acuity of the right eye was 6/6 and left eye was 6/8.6. The right eye was unremarkable, and both eyes were phakic. Some whitish keratotic precipitates were

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found over the left eye with cell 1 + shown in the anterior chamber. Dilated fundus examination revealed macular edema over the left eye with normal optic disc, and there was no vitreous opacity. Uveitis, suspect RA related, was initially impressed, and topical 1% prednisolone acetate (dosage: every 2 h) was prescribed first, and laboratory tests (included serum tests for syphilis, human immunodeficiency virus, *Toxoplasma*, herpes simplex virus, cytomegalovirus and varicella zoster virus, and chest X-ray) showed no other etiology identified for uveitis, except underlying RA. There was no systemic medication added, and no sub-Tenon's or intravitreal corticosteroid was using toward the uveitis.

One-week later, uveitis resolved as a silence of anterior chamber reaction, so the topical 1% prednisolone acetate was gradually tapered to twice daily. However, blurred vision in the left eye still complained. Severe macular edema was confirmed by optical coherence tomography (OCT) (central macular thickness [CMT] as 595 μm) [Figure 1a]. There was neither other possible cause explaining the persistence of macular edema due to lack of related retinal disease found nor any newly added topical or systemic medication. With the suspect of hydroxychloroquine-related toxicity, we advised the rheumatologist to discontinue hydroxychloroquine (The sulfasalazine was also held and leflunomide was added). Her symptoms improved gradually after cessation of hydroxychloroquine, and further serial image study confirmed subsiding of the macular edema without any further treatment [Figure 1b-d]. The vision improved with the resolution of macular edema correspondingly after cessation of hydroxychloroquine [Figure 2]. OCT showed the CMT was 249 μm 4.5 months after discontinuation of hydroxychloroquine. Fluorescein angiography was not done due to her history of drug allergy. There was no typical sign of hydroxychloroquine retinopathy through the whole course.

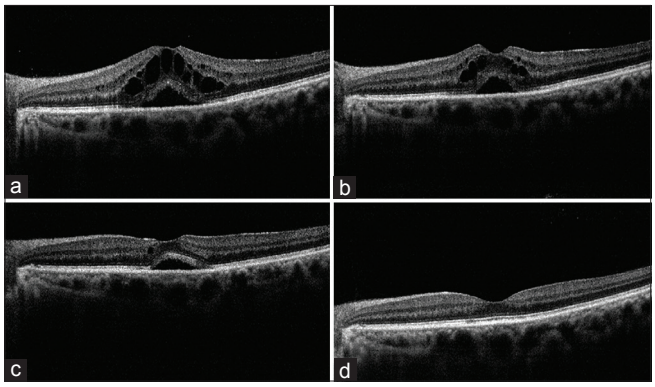

Figure 1: Serial optical coherence tomography studies after cessation of hydroxychloroquine. (a) Baseline before cessation of hydroxychloroquine; central macular thickness: 595 μm, (b) 2 weeks later; central macular thickness: 473 μm, (c) 5 weeks later; central macular thickness: 339 μm, (d) 18 weeks later; central macular thickness: 249 μm

Discussion

Hydroxychloroquine, a derivative of chloroquine, was first used as an antimalarial agent and subsequently played an important role for the long-term treatment of systemic lupus erythematosus, RA, and other autoimmune conditions. Despite less than chloroquine,[2] hydroxychloroquine still has retinal toxicity. The incidence of retinal toxicity is very low, but it may result in irreversible visual loss. Common presentation of toxicity was a subtle granular depigmentation of the paracentral RPE (with bilateral paracentral visual field changes) and then progressed to bull's-eye maculopathy (with paracentral scotomata), and even cause widespread retinal atrophy and visual loss in severe cases. The mechanism of hydroxychloroquine toxicity is not completely understood. It may be involvement of the RPE where the drug binds to melanin, adversely influence the metabolism of the retinal cells, and may lead to the slow and chronic toxic effects.[3]

Macular edema may develop in various retinal diseases such as diabetic retinopathy, vascular occlusions, postsurgical situations, and inflammatory conditions. It also can be induced by various systemic and local medications such as thiazolidinediones, fingolimod, tamoxifen, taxanes, niacin, and interferons. Ophthalmologic pharmaceutical agents, such as prostaglandin analogs, epinephrine, timolol, and ophthalmic preparation preservatives, have also been reported to cause macular edema as an adverse event.[4] The key pathophysiologic process is a breakdown of the blood–retinal barrier, normally preventing water movement in the retina, thus allowing fluid to accumulate in the retinal tissue through special water fluxes. Inflammatory processes and an increase in vascular permeability play a central role.

Despite numerous literature of retinal toxicity of chloroquine and hydroxychloroquine, there were a few

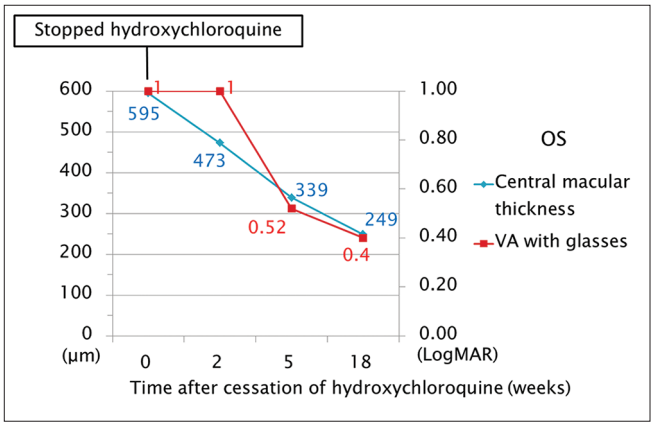

Figure 2: Vision improved with the resolution of macular edema correspondingly after cessation of hydroxychloroquine

previous formal reports of macular edema formation. In an early case series of chloroquine retinopathy reports, 5/78 patients have macular edema.[5] Kellner *et al*. also reported four cases of cystoid macular edema formation after chloroquine/hydroxychloroquine cessation for at least 2 years, which was thought to be associated with the ongoing degenerative process and not drug associated.[6] Although earlier surveys of patients taking hydroxychloroquine found that the risk of toxicity depended on cumulative exposure (using the drug for more than 7 years or with a cumulative dose that exceeds 1000 g), recent literature suggested that daily doses be limited to 5.0 mg/kg hydroxychloroquine, calculated on the basis of real body weight.[7] Our patient received hydroxychloroquine in the dosage of 400 mg/day (equal to 6.90 mg/kg [body weight] daily) irregularly for 18 months with accumulative dose as 145.6 g. The cumulative exposure was not high, but daily dose was over the safety limit. In this expect, there was possible for our patient to get hydroxychloroquine-related toxicity.

In our case, the initial presentation included anterior uveitis and macular edema, which was considered as RA-related uveitis and secondary macular edema. However, macular edema persisted even after the resolution of anterior uveitis and resolved only after cessation of hydroxychloroquine. Although there was no typical presentation of hydroxychloroquine retinopathy, hydroxychloroquine-related retinal toxicity was impressed based on the clinical course. The possible pathogenesis of macular edema caused by hydroxychloroquine might be related to alteration of blood–retinal barrier, which resulted from RPE damage caused by hydroxychloroquine due to its toxicity and resulted in fluid accumulation. The symptoms improved dramatically after cessation of hydroxychloroquine, with decreased macular edema, followed by image studies, so it seemed like the process was reversible. However, further follow-up was still needed due to possibility of progression of retinopathy even after cessation of the medication reported by the previous literature. Till date, there was no report of hydroxychloroquine-related uveitis. We are not sure whether uveitis and macular edema are both induced by hydroxychloroquine or just coincident. Although macular edema may persist after resolution of uveitis, the dramatic change after cessation of the hydroxychloroquine in our case still highly indicated the possibility of relation between the hydroxychloroquine and macular edema. Simultaneously, sulfasalazine was also held and leflunomide was added, but no previous literature reported macular edema caused by sulfasalazine or treated by leflunomide. Her clinical presentation did favor the possibility that the uveitis is RA related and hydroxychloroquine exacerbated the formation of macular edema.

With the increased indications of hydroxychloroquine, ophthalmologists are expected to meet more challenge of related retinal toxicity. Early diagnosis and proper management is the key to save the vision. With the insidious onset and subtle change of fundus, both patients and physicians should be aware of the risk and symptoms of toxicity, and annual examination is needed.[7] New tests of screening of hydroxychloroquine retinopathy using multifocal electroretinogram, spectral domain OCT, and fundus autofluorescence can be more sensitive than visual field and are currently recommended for baseline and monitoring.[8,9] In case of unexplained visual loss, awareness of medication-related complication should always be in mind.

Conclusion

Except the well-known signs of the retinal toxicity, macular edema might be a rare presentation of hydroxychloroquine-related retinal toxicity, and the condition may be reversible after cessation of the drugs.

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Conflicts of interest
The authors have no conflicts of interest to declare.

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