• Letter to the Editor •

Early-onset bull's eye maculopathy due to hydroxychloroquine in rheumatoid arthritis and myasthenia gravis

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Dear Editor,

We present the reported case of rapid onset bull's eye maculopathy.

Chloroquine (CQ) and its safer, more widely used analogue, hydroxychloroquine (HCQ), were originally developed as antimalarial medications. However, they have since become essential in the treatment of various autoimmune disorders due to their anti-inflammatory and immunomodulatory properties. HCQ is also being investigated for potential applications in diabetes mellitus, coronavirus disease 2019, heart disease, and as an adjunct in cancer therapy[1-2].

The most significant adverse effect of long-term HCQ/CQ therapy is irreversible retinal toxicity, which can lead to serious vision loss that may progress for several months after discontinuation of the drug[1]. A demographic study from 2014 found that the overall prevalence of HCQ retinopathy could be as high as 7.5%, significantly influenced by the daily dose relative to body weight and duration of use[3-4]. Other important risk factors include systemic diseases, concurrent use of tamoxifen, underlying retinal conditions, older age, and genetic predispositions to drug toxicity[1].

Various mechanisms have been proposed to explain HCQ retinopathy, with the most notable being the drug's binding to melanin pigments in the retinal pigmented epithelium (RPE). This interaction leads to drug accumulation and prolonged toxic effects, ultimately resulting in RPE damage and subsequent photoreceptor loss[5].

The study was conducted in accordance with the principles of the Declaration of Helsinki. The authors confirm that they have obtained informed consent from the patient. The patient has agreed to the reporting of her clinical information and images in this article. The patient understands that her name and personal identity will not be disclosed.

A 40-year-old woman from Ahvaz, Iran, presented with a complaint of painless bilateral vision loss that had persisted for 22y. She had a medical history of rheumatoid arthritis, diagnosed at age 8, and had been receiving treatment since age 16. Her regimen included continuous therapy with prednisolone, non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen and indomethacin, methotrexate, and a daily dose of 400 mg (4.4 mg per kg of actual body weight per day) of HCQ for approximately 48mo, resulting in a cumulative dose of 576 g. Prior to the initiation of HCQ therapy, her baseline ophthalmologic examination based on the written medical records indicated that she had no visual disturbances, with a best corrected visual acuity of 20/20 in both eyes.

After 48mo of HCQ therapy, the patient developed visual symptoms, prompting the discontinuation of the medication. Her disease remained medically controlled until the age of 36, when she began to experience diplopia and recurrent shortness of breath, leading to a diagnosis of myasthenia gravis.

She underwent several episodes of plasmapheresis, thymectomy surgery, and was treated with pyridostigmine. At the time of her examination, the patient weighed 70 kg (approximately 90 kg during her HCQ use) and had no history of liver or renal dysfunction. There was a positive family history of type 1 diabetes mellitus, myasthenia gravis, and Behçet's disease in her older sister.

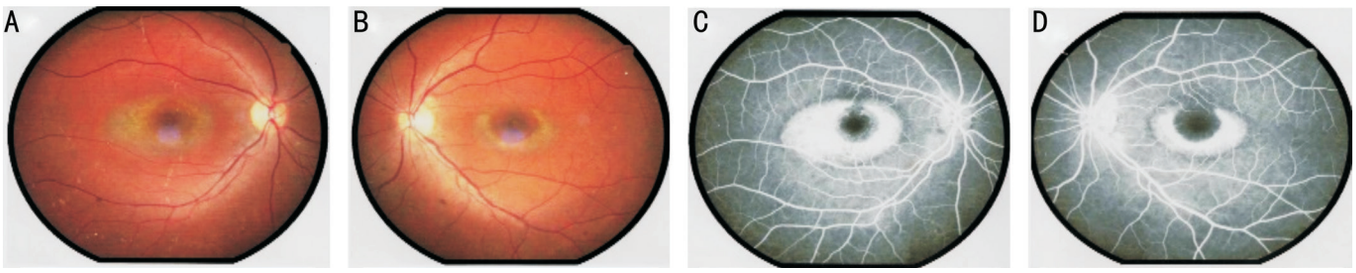

Figure 1 Fundus photography and fluorescein angiography of the patient A (Right eye) and B (left eye): Fundus image demonstrating characteristic bull's eye maculopathy with central atrophic areas and surrounding RPE changes. C and D: Fluorescein angiography showing late-phase hyperfluorescence in the foveal region, indicating compromised retinal integrity. RPE: Retinal pigmented epithelium.

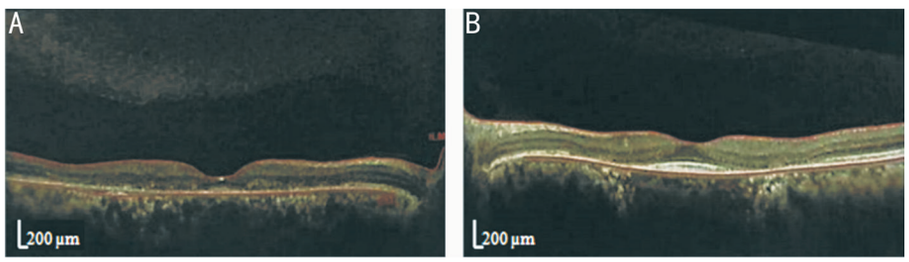

Figure 2 Macular OCT findings Right eye (A) and left eye (B) OCT images display a characteristic "flying saucer" pattern in the left eye. OCT: Optical coherence tomography.

Upon ophthalmologic examination at the time of presentation, her visual acuity was 20/25 in the right eye and 20/50 in the left eye, with best corrected visual acuity of 20/20 in the right eye and 20/50 in the left eye using the E-chart. Her pupils were symmetric, showing no relative afferent defect. Ocular motility testing was within normal limits across all gazes, and no ptosis was observed. A slit lamp examination of the anterior segment was normal in both eyes. Goldmann applanation tonometry measurements showed intraocular pressures of 11 mm Hg in the right eye and 12 mm Hg in the left eye.

Fundoscopic examination revealed a regular oval ring of hypopigmentation in the RPE with a characteristic Bull's eye appearance at the macula of both eyes. The optic nerve head and retinal periphery appeared normal bilaterally.

Fluorescein angiography of both eyes demonstrated a parafoveal ring of hyper fluorescence (window defect) surrounding a central area of hypo fluorescence (blockage), consistent with bull's eye maculopathy (Figure 1). Retinal imaging conducted *via* optical coherence tomography (OCT Spectralis, Heidelberg Engineering, Germany) revealed foveal and parafoveal outer retinal defects affecting the inner segment/outer segment junction, external limiting membrane, and RPE in both eyes, which was consistent with the flying saucer pattern in the left eye (Figure 2). Standard automated perimetry (HFA II; Humphrey Instrument Inc., USA) indicated the presence of bilateral central scotomas.

The overall risk of HCQ maculopathy is generally reported to be below 1% for use up to 5y, below 2% for usage up to 10y, and approximately 20% after 20y of HCQ therapy. According to the 2016 American Academy of Ophthalmology revised guidelines, it is recommended that the safe daily dose of HCQ should not exceed 5 mg/kg of actual body weight, and cumulative total doses should ideally remain below 1000 g to optimize the benefit-risk ratio[1].

Current guidelines recommend a baseline fundus examination within the first year of HCQ use, followed by annual screenings after five years in patients at low risk for toxicity. However, many practitioners opt to screen patients every 6 to 12mo. The presented case, despite undergoing a baseline examination, did not receive ophthalmologic evaluation during the four years of HCQ use until symptoms of vision loss emerged. Annual follow-up examinations alongside patient education on the alarm signs of drug toxicity could prevent the occurrence of ocular complications associated with this medication[1].

The primary predictors of HCQ-induced retinopathy include the dosage of the medication, pre-existing retinal conditions, impaired kidney or liver function, and advanced age[1,6]. Although these significant risk factors were absent in our patient, she still exhibited signs of HCQ toxicity, suggesting potential contributions from other unrecognized factors.

Genetic predispositions or acquired vulnerabilities to HCQ toxicity may be implicated. Variations in the cytochrome P450 genes, which metabolize HCQ, might influence its blood concentration and subsequently enhance the risk of adverse reactions[7-9].

Another factor that may have contributed to the early onset of retinal toxicity in this patient is the concurrent use of HCQ with NSAIDs such as naproxen and indomethacin. Both HCQ

and NSAIDs are metabolized in the liver through cytochrome P450 enzymes[10-11].

The effect of the patient's extensive personal and familial history of autoimmune diseases on her retinal condition is also worth exploring. Autoimmune retinopathy could play a role in her underlying eye disease. Moreover, both CQ and HCQ have been associated with proximal myopathy, neuropathy, and drug-induced myasthenia gravis[12].

In this patient, the severe myasthenic symptoms arose approximately 18y after ceasing HCQ therapy, which appears more aligned with her background of autoimmunity than with drug-induced myasthenia.

As conclusion, regular screening for HCQ retinopathy, including comprehensive ophthalmic assessments, spectral-domain OCT, and visual field tests, is essential for early detection and improved long-term visual outcomes. The American Academy of Ophthalmology recommends a baseline eye evaluation before starting HCQ, with annual follow-ups beginning in the fifth year of treatment, and earlier screenings if risk factors are present, such as renal disease or tamoxifen use.

This case emphasizes the need for increased patient education on drug toxicity symptoms and further research to refine screening guidelines and identify additional risk factors for earlier intervention.

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