Optical coherence tomography angiography features in a case of hydroxychloroquine retinopathy


Recently, with the introduction of OCT angiography (OCTA) in the clinical practice, a device that allows three-dimensional imaging of retinal and choroidal microvasculature, there has been increasing interest in investigating the efficacy of OCTA as a screening tool in HCQ retinopathy. The vast majority of the reports reveal a diminution of the vessel density (VD) of both retinal and choroidal microvasculature in patients taking HCQ for more than 5y\(^7\). Nonetheless, there are no reports that analyze OCTA retinal features in patients with a confirmed diagnosis of HCQ retinopathy.

The aim of our case report is to analyze multimodal imaging findings (including OCTA characteristics) in a case of HCQ retinopathy to improve our knowledge about pathogenic mechanism of HCQ retinal toxicity.

CASE REPORT

A 41-year-old female presented to her annual checkup. She was on treatment with HCQ 400 mg per day because a systemic lupus erythematosus since 11 years ago. She had a history of lupus nephritis treated with peritoneal dialysis in the last year. She was in treatment with epoetin alfa 3.000 IU/0.3 mL each 10d, amlodipine 10 mg per day, telmisartan 40 mg once a day, furosemide 40 mg per day, omeprazole 20 mg once a day, sevelamer carbonate 2400 mg twice a day and vitamin D.

Informed consent for publication was acquired, following the tenets of the Declaration of Helsinki.

Best-corrected visual acuity (BCVA) was 20/25 Snellen equivalent in the right eye (OD) and 20/20 Snellen equivalent in the left eye (OS). The intraocular pressures and anterior segment examination were unremarkable in both eyes (OU). Fundus examination showed a slight central mottling of the retinal pigment epithelium (RPE) and the “flying saucer” sign (which consists in a perifoveal thinning of the ONL with an associated displacement of the inner retinal structures toward the RPE and a variable loss of the normal foveal depression)\(^2,4,6\).

With the development of OCT, an objective examination that provides high-resolution images of retinal layers, an early detection of preclinical pathologic changes secondary to HCQ retinopathy has been enabled. OCT signs of HCQ retinopathy include perifoveal loss of the ellipsoid zone (EZ), disruption of the external limiting membrane (ELM), thinning of the outer nuclear layer (ONL), granular appearance of the retinal pigment epithelium (RPE) and the “flying saucer” sign (which consists in a perifoveal thinning of the ONL with an associated displacement of the inner retinal structures toward the RPE and a variable loss of the normal foveal depression)\(^2,4,6\).

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perifoveal thinning of the ONL, and RPE damage manifested with a granular appearance of the RPE and the double-layer sign in OU (Figure 1E and 1F). OCTA imaging revealed the absence of damage in both superficial and deep retinal capillary plexus and in the choriocapillaris (CC) in OU. Nonetheless, OCTA showed an enlargement of the foveal avascular zone (FAZ) area in the superficial capillary plexus of OU. FAZ area of the OD and the OS was 599 and 529 µm, respectively (Figure 2). Humphrey 10-2 VF testing illustrated non-specific VF defects in OU (Figure 3).

A diagnosis of HCQ retinopathy was confirmed. Thus, rheumatologists were advised to discontinue HCQ.

**DISCUSSION**

The mechanism of HCQ retinal toxicity is unclear. It has been shown that HCQ binds to melanin within melanin-rich ocular tissues (including iris, ciliary body, RPE, and choroid). Moreover, it is thought that HCQ affects the metabolism of retinal cells, as animal experiments have demonstrated that the drug can affect all retinal layers.\(^7\text{-}^{10}\)

Multimodal imaging findings in HCQ retinopathy support that HCQ damages primarily the outer retina. OCT signs of HCQ retinal toxicity include perifoveal loss of the EZ, ELM disruption, thinning of the ONL, and hyperreflective material that originates in the RPE and extends vertically into the inner retinal layers (including the outer plexiform layer and the ONL).\(^2\text{-}^{6},^{11}\) It is still unknown whether RPE damage results from direct HCQ toxicity to RPE cells or secondarily from adjacent photoreceptor death. RPE damage is not usually seen.
until the overlying photoreceptors (PR) are destroyed, typically demonstrated as EZ disruption and ONL thinning. Nonetheless, this does not rule out the direct toxic effect of HCQ on RPE. In fact, it is well known that HCQ binds to melanin-rich ocular tissues such as the RPE. In our case, we could demonstrate an enlargement of the FAZ area in the SCP, which is probably secondary to HCQ binding to melanin-rich tall RPE cells. RPE cells are responsible for the formation of FAZ. Thus, we suggested that HCQ has a direct toxic effect over the RPE. In fact, this enlargement of the FAZ has been demonstrated in patients taking HCQ with no signs of HCQ retinopathy, so we suggested that RPE damage may be the onset of outer retinal degeneration[7,10].

HCQ has a lipofuscinogenic nature, but the hyperreflective material that invades the outer retina causing a double-layer sign remains poorly understood. It is thought that this hyperreflective material may be the result of pigment migration from the RPE into the retina or may be secondary to macrophages recruitment by the damaged RPE to remove outer retinal debris[11]. In our case, hyperreflective material corresponded with the areas of hypoautofluorescence demonstrated by FAF. However, the perifoveal atrophy of RPE may be the most probably cause of this hypoautofluorescence. RPE is essential in maintaining the integrity of PR. Because of that, once RPE function is compromised by HCQ, PR start a continual degeneration that leads to EZ disruption and ONL thinning[10]. The double-layer sign may be formed by fibrovascular tissue which tries to maintain cellular metabolic activity of PR, as occurred in type 1 neovascular membranes. However, OCTA did not reveal flow signal. Nevertheless, it is possible that flow signal is under the lowest threshold detectable by OCTA imaging.

It has been demonstrated that HCQ binds to melanin present in the choroid. Therefore, we would expect that HCQ causes damage in the CC, as was recently demonstrated by Halouani et al[12]. However, OCTA imaging of the CC was normal in our case. We suggested that venous drainage of the choroid promotes the clearance of the drug. Nevertheless, it has been shown that HCQ persists in the RPE due to its slow clearance, leading to the accumulation of lipofuscin and the persistence of the drug at the RPE[13]. Because of that, we suggested that the primary target of HCQ is the RPE, and PR get damaged secondarily to RPE atrophy. To the best of our knowledge, this is the second report that analyzes OCTA imaging in a case of HCQ retinopathy. OCTA demonstrated an enlargement of the FAZ in the superficial capillary plexus. Thus, we suggested that RPE atrophy may be the primary target of HCQ and the onset of outer retinal degeneration.

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