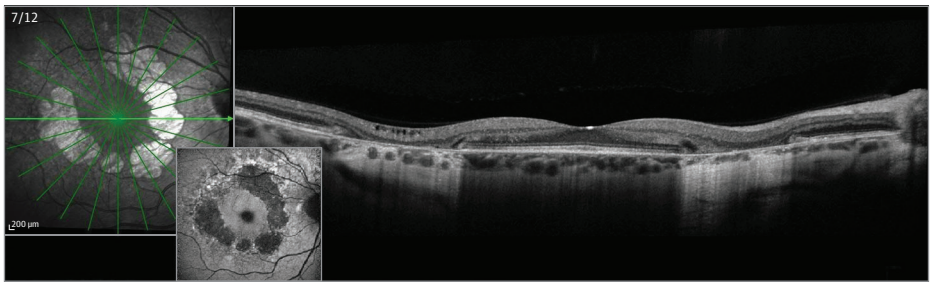
JAMA Ophthalmology Clinical Challenge

Bilateral Perifoveal Atrophy in a 46-Year-Old Woman

Reeda Bou Said, MD; Andrew J. Barkmeier, MD

A Left eye



B Right eye

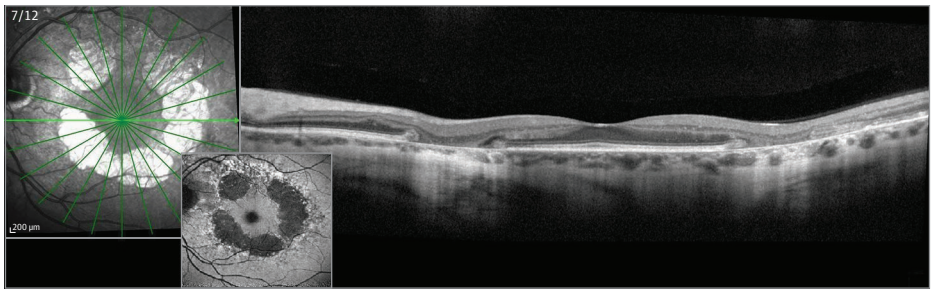


Figure. Spectral-domain optical coherence tomography and fundus autofluoresence imaging in the left (A) and right (B) eyes.

A 46-year-old woman was referred for a second opinion regarding hydroxychloroquine retinal toxicity. Her medical history included systemic lupus erythematosus (SLE), diabetes type 1, nonalcoholic steatohepatosis, mild congenital hearing loss, and anemia. SLE was managed with azathioprine and belimumab, and she had been taking hydroxychloroquine, 400 mg, daily for 5 years before the medication was recently stopped due to concern for retinal toxicity. Review of systems was notable for imbalance, cognitive decline, major depression, and recent onset of suspected seizures.

Snellen visual acuity was 20/30 OD and 20/20 OS and intraocular pressures were normal. Results of slitlamp examination of the anterior segment were unremarkable, with clear corneas, quiet anterior chambers, and clear lenses bilaterally. Fundus examination revealed bilateral discrete perifoveal circular areas of atrophy. The optic discs and fundus were otherwise unremarkable. Fundus autofluorescence and optical coherence tomography (OCT) revealed perifoveal hypoautofluorescence corresponding with complete retinal pigment epithelium and outer retinal atrophy on OCT (**Figure** and insert). Automated 10-2 visual field testing revealed dense paracentral ring scotomata bilaterally.

WHAT WOULD YOU DO NEXT?

A. Confirm hydroxychloroquine retinal toxicity and recommend observation when not receiving therapy

B. Recommend AREDS 2 supplementation

C. Intravitreal injection of a complement inhibitor

D. Genetic evaluation

CME Quiz at jamacmelookup.com

Diagnosis

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

What to Do Next

D. Genetic evaluation

Discussion

This patient's presentation was atypical for hydroxychloroquine retinal toxicity. Her pattern of perifoveal atrophy was more consistent with inherited mitochondrial disease, and ocular findings were discussed with neurology, medical genetics, and rheumatology teams in the context of progressive neurologic symptoms, which prompted genetic evaluation. Genetic testing revealed a pathogenic *MT-TL1* m.3243A>G sequence variation (heteroplasmy 23%), the most common variation causing mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS).

MELAS, while relatively rare in the general population, is one of the more common mitochondrial myopathies, with a population-dependent prevalence between 0.18 and 236 per 100 000 individuals.[1] Similar to other mitochondrial diseases, MELAS is either maternally inherited or may arise from de novo mitochondrial DNA (mtDNA) sequence variations, most commonly A to G transition at mtDNA position 3243.[2,3] Age at onset is variable but usually manifests before age 40 years with any combination of seizures, strokelike episodes, progressive cognitive deterioration, myopathy, and variable involvement of other organs.[1,4,5] Disease severity is impacted by heteroplasmy, the proportion of pathogenic mtDNA, and potentially by coexisting nuclear DNA sequence variations.[6] Potential associations include diabetes, sensorineural hearing loss, and cardiac disorders. The most common clinical presentation of retinopathy associated with *MT-TL1* m.3243A>G sequence variations is circumferential perifoveal atrophy, initially discontinuous, as in this patient, which may coalesce over time.[4] Fundus autofluorescence imaging typically demonstrates hypoautofluorescence in areas of advanced chorioretinal atrophy with surrounding speckled hyperautofluorescence. Other possible ocular manifestations include ophthalmoplegia, nystagmus, cataract, and optic nerve atrophy.[7] Visual acuity is variable but often good at presentation.[4]

Diagnosis of MELAS may be confirmed with genetic testing in the context of relevant clinical findings (including encephalopathy and strokelike episodes), laboratory clues (including elevated lactate levels in serum and cerebrospinal fluid [CSF]), and muscle biopsy evaluating for ragged red fibers. Comprehensive systemic evaluation is imperative for identification and management of associated conditions. Management of MELAS is mainly supportive and also critically involves avoiding medications that can cause mitochondrial toxicity (eg, valproic acid) or lactic acidosis (eg, metformin).[1] Multiple studies have supported a role for arginine supplementation in the management and prevention of strokelike episodes,[8] as well as for other vitamins and supplements including coenzyme Q10, creatine, and carnitine as part of a "mitochondrial cocktail" for patients with mitochondrial cytopathies.[9]

Option A is incorrect. While discontinuing hydroxychloroquine may be reasonable in the context of this patient's maculopathy,[10] further evaluation is warranted to make the appropriate diagnosis and to ensure appropriate monitoring, identification of associated systemic manifestations, genetic counseling, and potential evaluation of family members.

Options B and C are incorrect. While there is outer retinal and retinal pigment epithelium atrophy on OCT, the patient is relatively young and lacks other findings consistent with age-related macular degeneration.

Patient Outcome

The patient's systemic manifestations of MELAS were managed by her multidisciplinary health care team. Her evaluation revealed elevated lactic acid in the serum and CSF. Magnetic resonance imaging of the brain showed diffuse parenchymal volume loss for her age, with disproportionate cerebellum involvement and scattered chronic lacunar infarcts in the basal ganglia and left thalamus. She was prescribed arginine, carnitine, and coenzyme Q10, as well as vitamins A, D, E, K, and a vitamin B complex. She continued insulin treatment for her diabetes, lactulose, rifaximin, and sodium benzoate for cirrhosis-associated encephalopathy, as well as antiepileptic medication.

ARTICLE INFORMATION

Author Affiliations: Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota.

Corresponding Author: Andrew J. Barkmeier, MD, Department of Ophthalmology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (barkmeier.andrew@mayo.edu).

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