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Cystoid macular changes on optical coherence tomography in a patient with maternally inherited diabetes and deafness (MIDD)-associated macular dystrophy

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Abstract

The clinical presentation and optical coherence tomography findings in a patient with maternally inherited diabetes and deafness (MIDD) are presented to highlight the presence of macular cystoid spaces in some patients with this disease. Typically, patients with MIDD demonstrate progression of a pigmentary maculopathy into areas of geographic macular atrophy. At the time of initial visit, the 30-year-old patient had large macular cystoid changes in addition to retinal pigmentary changes in both eyes. The cystoid changes responded to treatment with systemic immunosuppression and a topical carbonic anhydrase inhibitor (CAI), recurred when treated with topical CAI monotherapy, and finally resolved after an intravitreal triamcinolone acetonide injection. Over time, the retinal atrophy continued to progress, but the macular cysts did not recur. The patient received systemic immunosuppression for renal transplantation due to renal failure resulting from focal glomerulosclerosis. There was no evidence of diabetic retinopathy at any time during the five-and-a-half-year follow-up, and the patient retained good visual acuity in both eyes.

Introduction

The m.3243A>G point mutation in mitochondrial DNA (mtDNA) can cause a spectrum of disease manifestations, including maternally inherited diabetes and deafness (MIDD) and the more severe mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). [1–9] Patients with MIDD typically present with a low body mass index, sensorineural deafness, and early adult-onset diabetes in the third or fourth decades. Patients with MELAS typically present in childhood or adolescence with short stature, migraine-like headache, stroke-like episodes, encephalopathy and/or seizures, dementia, ataxias, hearing loss, and mitochondrial myopathy. Other conditions associated with this mutation include short stature, cardiomyopathy, gastrointestinal dysmotility, chronic progressive external ophthalmoplegia, and renal failure. [10] Both MIDD and MELAS are known to have retinal

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

features, which have been described as a pigmentary retinopathy and/or macular atrophy. [3, 4, 11–16] The manifestation of macular cystoid spaces has not been well described in these conditions. It was previously thought that MIDD only led to atrophic retinal changes akin to the findings in pattern-like dystrophy or macular degeneration. We describe a patient with MIDD who presented with bilateral intraretinal cystoid macular changes on optical coherence tomography (OCT), which responded to local and systemic treatment with excellent preservation of vision despite progression of her atrophic disease.

Case report

A 30-year-old female patient was referred to our clinic for a diagnosis of a possible hereditary retinal dystrophy after she was found to have macular pigmentary changes on routine examination (Figure 1a). Primary medical history was significant at this time for asthma, migraines, and hearing loss. The proband also has an older sister with a history of migraine, thromboembolic events and chronic fatigue. There is an extensive history of early onset adult diabetes within the maternal lineage (3 maternal uncles and a maternal aunt). There was no family history of high myopia. At presentation, the patient was found to be myopic with a refractive error of -6.75 OD and -7.00 OS. Her visual acuity was 20/40 OU. Optic nerves were slightly pale with a cup to disc ratio of 0.3 OD and 0.2 OS. The vessels were of normal caliber. Fundi of both eyes showed multiple areas of retinal pigment epithelium (RPE) atrophy, with RPE mottling centrally and baring of underlying choroidal vessels. Goldmann visual field demonstrated minimal constriction (Figure 2). In an electroretinogram (ERG), the right eye amplitudes were subnormal with a slight increase in the implicit time on the rod isolated ERG. The left eye showed an abnormal photopic ERG that was approximately 60 percent of normal with a normal implicit time while the rod isolated ERG was approximately 30 percent of normal with prolonged implicit time (Figure 3). Large intraretinal cystoid spaces in the fovea were visualized on spectral domain OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) (Figure 4a). Of note, these cystic spaces did not show leakage on fluorescein angiography. Fundus autofluorescence showed a corresponding pattern of mottling with hyperfluorescent areas of retinal atrophy interspersed with areas of hyperfluorescence on the leading edge of pigmentary change (figure 1c). A Western blot was performed on the patient's serum, and 8 bands corresponding to anti-retinal antibodies (50kDa, 70kDa, 75 kDa, 100kDa, 110kDa, 120kDa, 145kDa, 160kDa) were detected (Figure 5). Based on the clinical presentation, the patient was started on oral prednisone 10mg QD, Imuran 50mg BID and topical dorzolamide TID OU. At the follow up visit 4 months later, spectral domain OCT demonstrated drastic reduction of the macular cysts, and vision improved to 20/25 OU (Figure 4b). This constellation of manifestations led to screening for mitochondrial mutations and the detection of an m.3243A>G mutation in the mitochondrial tRNA^{-Leu(UUR)} gene in the blood. Following these diagnoses, the immunosuppressive treatment was tapered over the next two months. Despite the fact that the patient continued on the CAI, macular cysts recurred in both eyes eighteen months later. This was associated with a nodular RPE elevation and a visual decline to 20/70 OD (Figure 4c). The decrease in vision in the right eye was treated with an intravitreal injection of triamcinolone acetonide (IVTA). Her vision improved to the 20/40 level OU after injection, with resolution of the cystoid spaces and

pigment epithelial elevation (Figure 4d). Six months later, she underwent renal transplantation and was restarted on concurrent immunosuppression with cyclosporine 100mg BID and everolimus 1mg po BID. Five years after initial presentation, her vision was 20/25 OD and 20/30 OS, and she was maintained only on systemic immunosuppression because of her renal transplant. Macular changes had coalesced to become nummular areas of RPE atrophy (Figure 1b–c). The macula was devoid of any signs of diabetic retinopathy. New generation spectral domain Spectralis OCT (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) was used thereafter and demonstrated further disintegration of the ellipsoid zone in both maculae. The underlying RPE was disorganized, with patchy areas of thickened interdigitation zone. There was no recurrence of intraretinal cystoid spaces at the last follow up visit, which was 2 years after IVTA treatment. (Figure 4e). A summary of her clinical course can be found in Figure 6.

Discussion

MIDD is most often associated with ocular pigmentary maculopathy, retinal pigment epithelium mottling and drusen formation. [11] The phenomenon of cystic retinal changes in these patients is not well characterized in literature. It is possible that intraretinal cystoid macular degeneration in MIDD/MELAS is more common than was previously known. Early time-domain OCT resolution used in those studies might have been too low to detect subtle cystoid macular degeneration and to accurately detect response to treatment. It is also possible that the manifestation of macular cystoid spaces is a transient finding that occurs at an earlier stage in disease and may precede the well described punched out atrophic macular lesions seen in later disease stages.

The pathogenesis for the formation of these cysts in MIDD needs further elucidation. One previous report by de Laat et al. noted that a patient with an m.3243A>G mutation had transient cystoid spaces without leakage, which resolved with topical non-steroidal anti-inflammatory treatment. [12] Cystic changes without leakage on FA are seen in a number of retinal dystrophies, including retinitis pigmentosa, enhanced S cone syndrome and X-linked retinoschisis. The mechanism may represent a combination of structural abnormality in the integrity of macular architecture, a failure of the RPE pump, or a secondary response to the toxic byproducts liberated by the degenerative retina [13]. In MIDD, due to the development of type 2 diabetes mellitus, it is theoretically possible to develop diabetic macular edema (DME), which could mimic cystoid macular degeneration on OCT. However, DME can be differentiated from cystoid macular degeneration by its leakage on FA. In addition, several case reports suggest that mitochondrial mutations may have a protective effect against diabetic retinopathy. [14–19]

In treating the macular cystoid changes in our patient, we employed several agents. Topical carbonic anhydrase inhibitors and intravitreal corticosteroids are mainstay treatments for cystic changes in retinal dystrophies. [20] Several studies have demonstrated that patients with retinitis pigmentosa and cystoid macular edema with multiple anti-retinal antibody bands responded well to immunosuppression, resulting in visual gain. [21, 22] Antiretinal antibodies have never been previously described in patients with the m.3243A>G point mutation. This is most likely due to the fact that this was believed to be a mostly

progressively atrophic disease and autoimmune processes had not been previously contemplated as a mechanism of disease. In the case of our patient, it was the presence of cystoid changes which cued the investigations unto a search for biomarkers of autoimmunity. [22–24] While our patient demonstrated multiple bands on Western blotting against retinal protein, the exact contribution of these antibodies to the disease pathogenesis is unclear. Nevertheless, treatment appears to have been beneficial, since the retinal cysts responded dramatically to treatment, and sustained visual improvement was achieved. It is also suggested that asymptomatic relatives of probands may warrant regular ophthalmic and audiology assessments, such as in our case for the proband's sister who does manifest symptoms of migraine, thromboembolic events and chronic fatigue. Relatives may have subclinical fundusoscopic abnormalities and hearing loss that may progress with age and time, and hence early diagnosis may aid in management of anticipated health problems in this particular spectrum of mitochondrial disease.

Conclusion

Cystoid macular changes may occur in patients with the m.3243A>G mtDNA point mutation and MIDD. Although the pathophysiology and prevalence these changes are currently unknown, confirming and documenting their presence through imaging on OCT is important, since early diagnosis and management may lead to earlier visual improvement and may delay progression of visual acuity decline.

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Figure 1.

A) Fundus photography with pigment clumping in the macula at time of initial presentation
B) Fundus photography at last presentation, 5.5 years after initial photographs. Note the well-circumscribed punchedout peripapillary atrophy sparing the fovea. C) Autofluorescence photographs at last presentation. Note the hyperfluorescent borders and central areas of coalescing hypofluorescence. 607x795mm (100 x 100 DPI)

Figure 2. Goldmann perimetry demonstrating minimal field constriction in both eyes.!! + The isopters are indicated by in the boxes and labeled by color. !! +

Figure 3.

Left column: amplitudes and waveform in a normal subject. Middle and right columns: amplitudes and waveform of right eye and left eye respectively in our patient. The right eye amplitudes were subnormal with a slight increase in the implicit time on the rod isolated ERG. The left eye showed an abnormal photopic ERG that was approximately 60% of normal with a normal implicit time while the rod isolated ERG was approximately 30% of normal with prolonged implicit time. 254x190mm (72 x 72 DPI)

Figure 4. CMT: central macular thickness; VA: Visual acuity

A) OCT of both eyes at time of initial presentation

B) OCT of both eyes at four months after starting systemic immunosuppressive agents and topical dorzolamide OU

C) OCT at 3-year follow. Visual decline OD correlated with recurrent cystoid spaces and retinal pigment epithelium thickening and disorganization. Both eyes were treated with topical corticosteroids and CAI and the right eye also received intravitreal triamcinolone acetonide

D) Resolution of the subretinal deposit complex OD and normalization of retinal contour 6 months after intravitreal injection OD

E) OCT OU 5.5 years after initial presentation. Note progressive RPE mottling, interdigitation zone thickening, presence of outer retinal tubulations and loss of the ellipsoid line OU. 252x337mm (96 x 96 DPI)

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Figure 5. Western blot run on patient's serum obtained at time of initial presentation. Band pattern of anti-retinal antibodies seen on the left column after 10 minutes of exposure. Right column is bovine retina (BR) protein as control. HR: human retina; KDa: kilodaltons

Figure 6.