Outer retinal tubulation and inner retinal pseudocysts in a patient with maternally inherited diabetes and deafness evaluated with optical coherence tomography angiogram

Koushik Tripathy, Barsha Sarma, Shahana Mazumdar

A 47-year-old lady (index case) with diabetes and deafness showed multiple oval circumferential areas of perifoveal atrophy in both eyes. Autofluorescence revealed areas of hypoautofluorescence. Optical coherence tomography (OCT) showed depression of inner retinal surface, inner retinal hyporeflective spaces (pseudocysts), disorganization/thinning of outer retina, outer retinal tubulation, loss of external limiting membrane, ellipsoid and interdigitation zone, and thinning of the retinal pigment epithelium and choriocapillaris. The patient was evaluated using OCT angiogram. Retinal lesions of her mother (68-year-old) were very obvious on autofluorescence imaging. The result of A3243G mutation in MTTL1 gene was positive in the index case confirming the diagnosis of maternally inherited diabetes and deafness (MIDD).

Key words: Maternally inherited diabetes and deafness, mitochondrial disease, outer retinal tubulation, pattern dystrophy, pseudocysts

Maternally inherited diabetes and deafness (MIDD) is a mitochondrially inherited genetic disease comprising 0.5% to 2.8%[1] of the population with type 2 diabetes mellitus. Approximately 86% of patients have macular involvement.[1] Two patterns of macular involvement have been described in MIDD- (1) (more common) discontinuous perifoveal nummular atrophy with circumferential distribution, and (2) a pattern dystrophy (retinal pigment epithelial/RPE granularity, pigment clumping and pale deposits at the level of the RPE, without any significant atrophy).[2] Herein, we describe an Indian family with MIDD, in which ocular examination played a crucial role in unearthing the systemic diagnosis.

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Case Reports

Case 1

A 47-year-old lady with short stature (145 cm) had type 2 diabetes mellitus for the last 20 years. She had a history of severe sensorineural hearing loss for 12 years and ischemic heart disease for 5 years. Her mother and maternal aunt had developed diabetes and deafness before the age of 40 years. Her siblings and son had no systemic complaints. The best-corrected visual acuity (BCVA) was 20/20p in both eyes (right eye -4.75 DS, left eye -5.00 DS). Anterior segment and intraocular pressure were unremarkable in both eyes. The fundus showed well-defined, round to oval areas of atrophy surrounding the fovea in a circumferential manner in both eyes [Fig. 1a and b] which is very similar to the ocular features of MIDD. Autofluorescence accentuated the appearance and showed sharply defined discontinuous areas of perifoveal hypoautofluorescence surrounded by speckled hyper autofluorescence which was not clinically obvious [Fig. 1c and d]. The OCT [Fig. 2a-c] showed depression of inner retinal surface, inner retinal hyporeflective spaces [pseudocysts, Fig. 2a and b, *], disorganization/thinning of outer retina, outer retinal tubulation (ORT) [Fig. 2b, <], loss of external limiting membrane, ellipsoid and interdigitation zone, and thinning of the RPE and choriocapillaris. OCT angiogram showed some reduced flow at the area temporal to the fovea in the superficial retinal slab [Fig. 3a] and artifacts showing superficial vessels due to retinal thinning in the deep retinal slab [Fig. 3b]. Outer retinal slab appeared to have 2 unmasking artifacts in the area of atrophy [Fig. 3c], and the choriocapillaris slab showed signal void areas at the uninvolved area along with unmasking of underlying choroidal vessels at the involved area [Fig. 3d]. The multifocal electroretinogram (mfERG) revealed reduced foveal and perifoveal amplitudes which were more depressed in the right eye [Fig. 3e] compared to the left eye [Fig. 3f].

Case 2

Mother of the index case was a 68-year-old female. She had posterior subcapsular cataract in both eyes (right > left). BCVA was 20/30 in the right eye and 20/20p in the left eye. She had barely visible RPE changes around the fovea and the optic disc [Fig. 4a and b] which became obvious with autofluorescence imaging [Fig. 4c and d]. Case 1 was noted to have A3243G mutation in MTTL1 gene using Sanger sequencing. Due to financial constraints, the genetic analysis of family members could not be performed.

Discussion

The occurrence of characteristic macular changes in this family with diabetes and deafness was a clue for MIDD[3] which was

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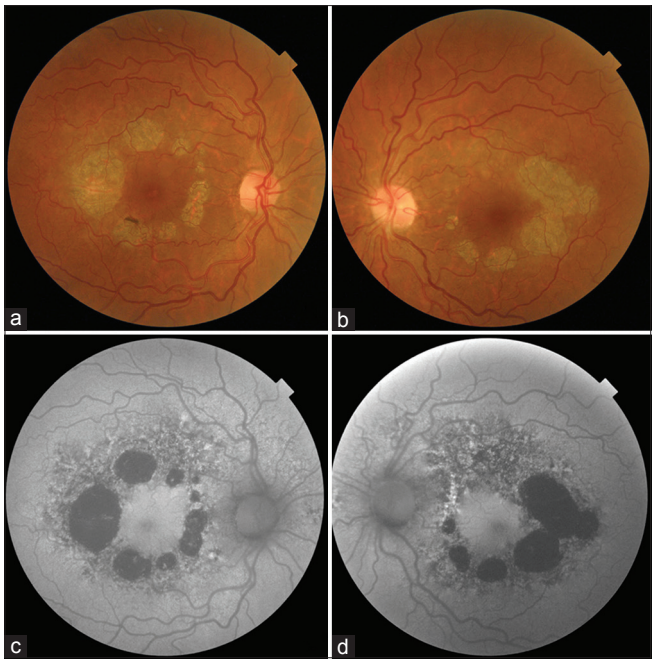

Figure 1: (a and b) The fundus photo of the right (a) and left (b) eye of case 1 showed multiple circumferential areas of atrophy. (c and d) The autofluorescence (AF) images of right (c) and left (d) eye showed sharply defined hypo-AF areas surrounded by speckled AF

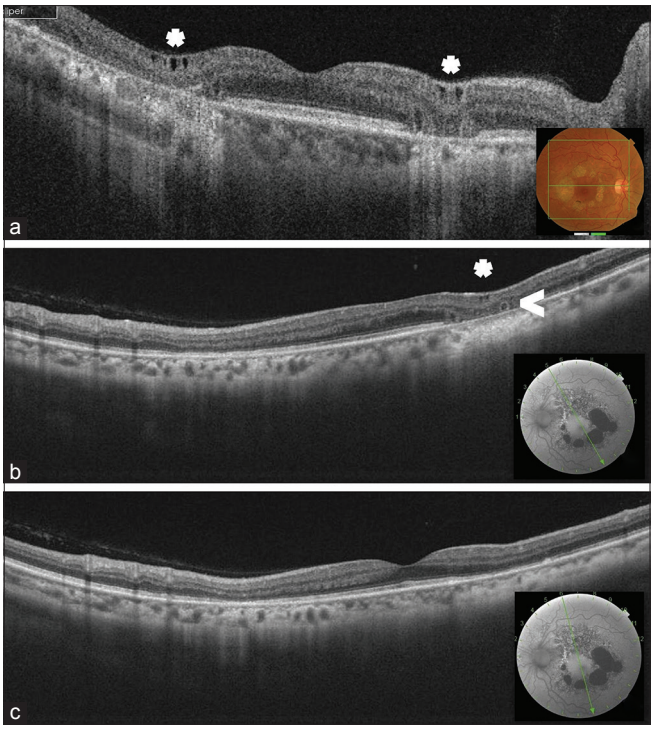

Figure 2: (a and b) The optical coherence tomography (case 1) of the right (a) and left (b) eye showed outer retinal thinning, choriocapillaris thinning, and increased penetration of the OCT laser light. Also, note the presence of intraretinal pseudocysts (*) and outer retinal tubulation (<). (c) shows a scan through the fovea

further confirmed by the presence of MTTL1 gene mutation in the index case. MIDD can be caused by mutation of multiple mitochondrial genes including MTTL1 (commonest), MTTE, and MTTK. A3243G mutation can also cause MELAS (mitochondrial encephalopathy, lactic acidosis, stroke-like episodes). The absence of systemic complaints in the siblings and son of the index case may be related to clinical variability due to heteroplasmy. However, they were advised a systemic evaluation for any occult disease.

Our patient had multiple areas of perifoveal atrophy on clinical exam, which was much more prominent with autofluorescence. The autofluorescence also showed speckled fluorescence around the clinically obvious lesions, which has been considered an important feature of MIDD.[2] Speckled autofluorescence which is more severe than clinical appearance is also noted in maculopathy due to dominant R172W (RDS) mutation.[2] However, unlike MIDD, the fovea is involved in R172W mutation and the autofluorescence changes are usually confined within the arcades and around the optic nerve.[2]

OCT showed inner retinal pseudocysts (hyporeflective spaces) in our case which is seen in 27% of eyes with geographic atrophy.[4] These small cystoid spaces were noted at the inner nuclear layer (41.6%), deep outer retinal layers (29.1%), in all retinal layers (12.5%), at the outer nuclear layer (12.5%), and just below the internal limiting membrane (4.1%) by Cohen and colleagues.[4] These were not associated with choroidal neovascular membrane (CNVM) and were hypothesized to be due to Muller cell degeneration[4] in atrophic age-related macular degeneration (AMD).

ORT has been reported in MIDD.[5,6] Zweifel SA and colleagues[6] were the first to describe ORT in neovascular AMD, CNVM in pseudoxanthoma elasticum and multifocal choroiditis and panuveitis, central serous chorioretinopathy, geographic atrophy, Bietti crystalline dystrophy, choroideremia, tissue inhibitor of metalloproteinase-3 negative pattern dystrophy, and 'retinal degeneration phenotypically consistent with a mitochondrial A3243G mutation'. ORTs appear as tubules which may be branching, straight, or composed of 'complex cavitary networks' on C scan OCT. On B scan OCT, ORTs appear as round or oval hyporeflective spaces surrounded by hyperreflective margins in the outer retina usually over areas of subretinal fibrosis or areas of retinal pigment epithelial abnormality.[6] ORT is a feature of degeneration of photoreceptors and does not require therapy. Pseudocyst and ORT in MIDD suggest that along with Muller cell degeneration there is photoreceptor degradation in the affected areas. ORT is limited only to the atrophic area.

OCT angiogram (OCTA) showed choriocapillaris voids before the development of the atrophy in MIDD.[7] Zhioua Braham and colleagues have described that OCTA 'showed foveal avascular zone enlargement, areas of retinal capillary rarefaction in superficial and deep capillary plexuses'.[8] In our patient, the choriocapillaris void areas were noted in the uninvolved foveal region as well as the atrophic regions to varying degrees, which may be indicative of progression of the disease. Features of progressive atrophy were noted in areas surrounding the patches on fundus photo image in the FAF image which was confirmed by OCTA.

Conclusion

In conclusion, the classic appearance helped us to the final diagnosis of MIDD and we describe the OCTA features of the disease.

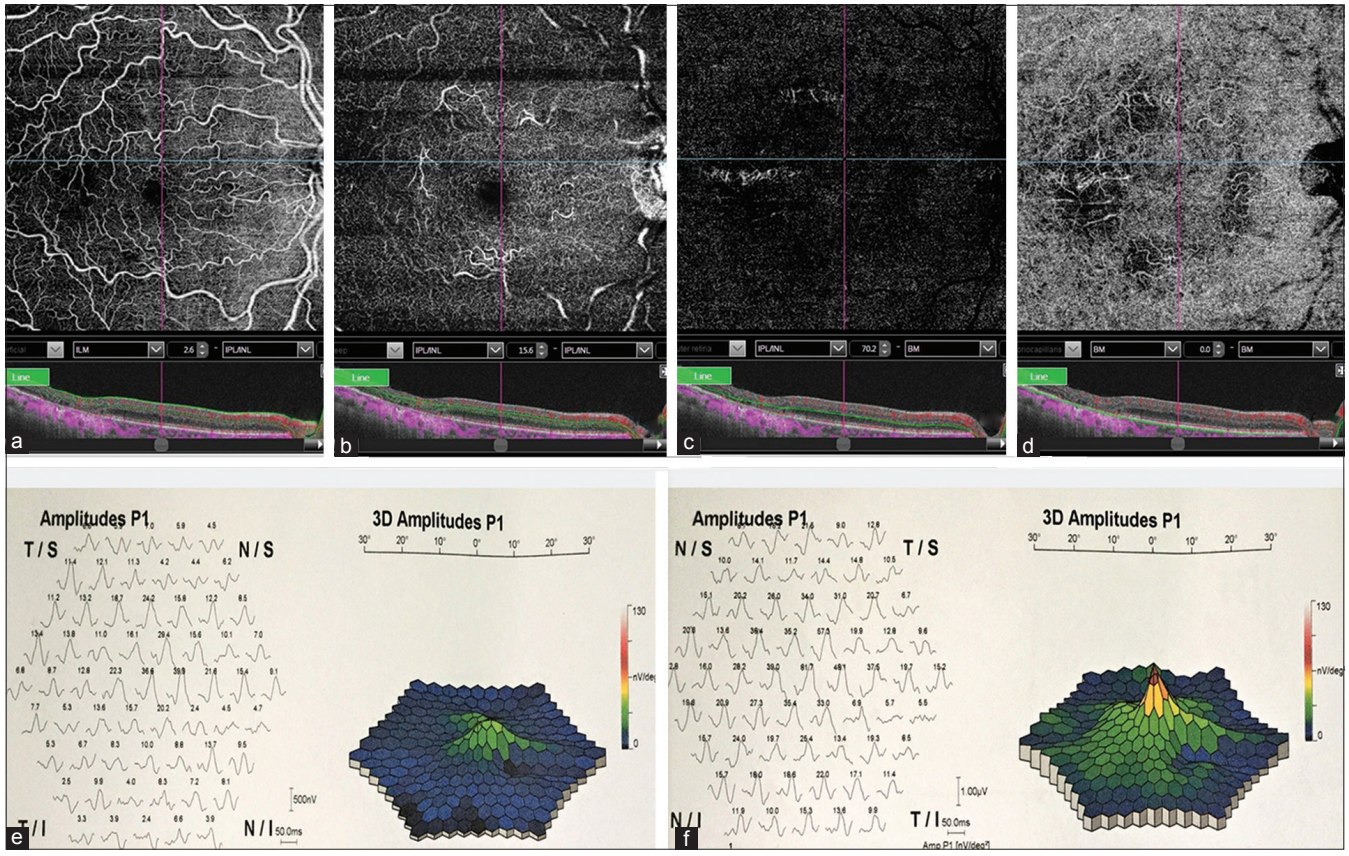

Figure 3: (a) The OCT angiography of case 1at the level of superficial retinal slab showed reduced flow temporal to the fovea. (b) The deep retinal slab artefactually showed superficial retinal vessels around the fovea. (c) The outer retinal slab showed unmasking of larger choroidal vessels. (d) The choriocapillaris slab showed hypoflow areas in the areas of atrophy as well as at the surrounding areas. (e and f) Multifocal electroretinogram of right (e) and left eye (f) showed reduced amplitudes

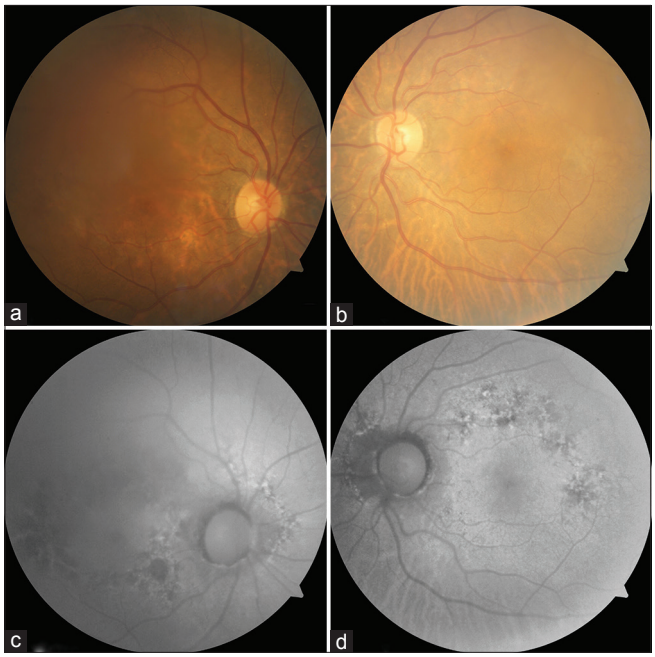

Figure 4: (a and b) The fundus of case 2 showed barely appreciable RPE changes in the right (a) and the left (b) eye. (c and d) Autofluorescence images made the RPE changes more obvious in both eyes (images are hazy due to cataract which was more in the right eye)

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Declaration of patient consent

Written informed consent for patient information and images to be published was provided by the patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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