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Obscured interdigitation zone at the early stage of gyrate atrophy: A case report

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ABSTRACT

Purpose: To report an early stage of gyrate atrophy (GA) of the retina and choroid for which spectral-domain optical coherence tomography (SD-OCT) images revealed an obscured interdigitation zone (IZ).
Observation: A 13-year-old boy was referred to our department due to blurred vision in his left eye. Best corrected visual acuity was 20/20 and 20/25 in the right and left eye, respectively. Fundus examination revealed scalloped atrophic peripheral chorioretinal lesions in both eyes. Concentrations of plasma and urine ornithine were 1192 nmol/mL and 1930 μmol/g·cre, respectively. Consequently, he was diagnosed with GA. Although Goldmann perimetry found no abnormalities, electroretinogram (ERG) revealed loss of the rod responses and significant attenuation of the cone responses in both eyes. Detailed analysis of the posterior part of the fundus using multifocal electroretinogram showed poor responses, specifically in the nasal macular area of the left eye. SD-OCT showed an obscured IZ corresponding to the attenuated cone response determined by ERG. There was preservation of the retinal pigment epithelium, ellipsoid zone and external limiting membrane.
Conclusions and Importance: Obscured IZ during early stage GA was confirmed in a teenage patient with a chief complaint of blurred vision. OCT is useful in the detection of minute morphological changes that occur earlier in GA.

1. Introduction

Gyrate atrophy (GA) is a rare, autosomal recessive, chorioretinal degenerative disease.[1] The primary cause is high levels of serum and urine ornithine due to a deficiency of ornithine delta-aminotransferase (OAT). Although the primary lesion in GA is thought to be atrophy of the retinal pigment epithelium (RPE),[2] the pathophysiological mechanism has yet to be fully understood, specifically during the early stages of the disease. GA has been classified into 4 stages depending on the area of the atrophy, which starts from the periphery and then moves toward the posterior pole.[3] Although OCT findings have been used to examine the advanced stages of GA, such as stage III or IV, reports on early stages, such as stage I or II, are seldom seen. Here, we report on the use of spectral-domain optical coherence tomography (SD-OCT) to detect an obscured interdigitation zone (IZ) during the early stage of GA, which corresponded to the attenuation of the cone responses in both eyes. However, results showed that the RPE was intact in the posterior pole.

2. Case report

A 13-year-old boy with no significant medical history was referred to our department due to blurred vision in the left eye. At the initial visit, best corrected visual acuity was 20/20 and 20/25 in the right and left eye, respectively. The refraction was −5.25 D Sph −1.50 D Cyl × 180 in the right eye and −5.25 D Sph −2.50 D Cyl × 180 in the left eye. Anterior examination identified slight posterior capsular cataracts. Ultra-widefield color fundus photograph (Optos ®200Tx; OPTOS PLC, Dunfermline, UK) revealed bilateral scalloped atrophic peripheral chorioretinal lesions in the patient's eyes (Fig. 1A and B). The fundus autofluorescence (FAF) image showed there was a decreased autofluorescence that corresponded to these atrophic lesions (Fig. 1C and D). Concentrations of plasma and urine ornithine were 1192 nmol/mL and 1930 μmol/g·cre, respectively, with both levels much higher than the reference values. Based on the clinical findings, serological and urine tests, the patient was diagnosed with stage II GA of the retina and choroid. The patient did not complain of nyctalopia. Although Goldmann perimetry (GP) found no abnormalities in both eyes (Fig. 2), the

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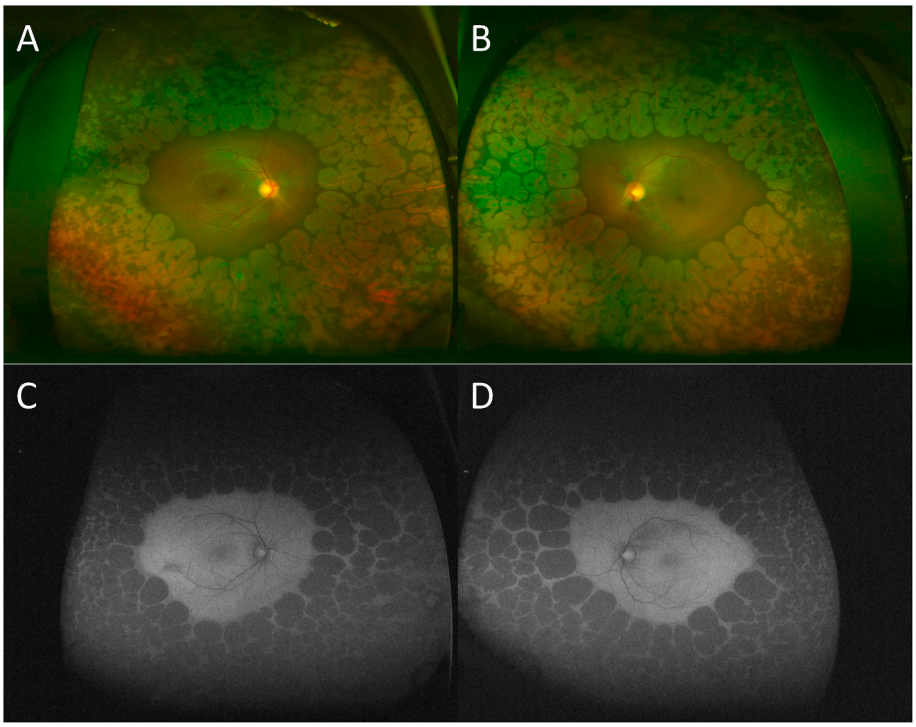

Fig. 1. Ultra-widefield fundus photographs. Ultra-widefield fundus photographs of the right eye (A, C) and left eye (B, D). Color fundus photographs show scalloped areas of chorioretinal degeneration appear in the periphery (A, B). These lesions have not yet reached the disc or the posterior pole. Fundus autofluorescence image (C, D) shows decreased autofluorescence corresponding to areas of chorioretinal degeneration.

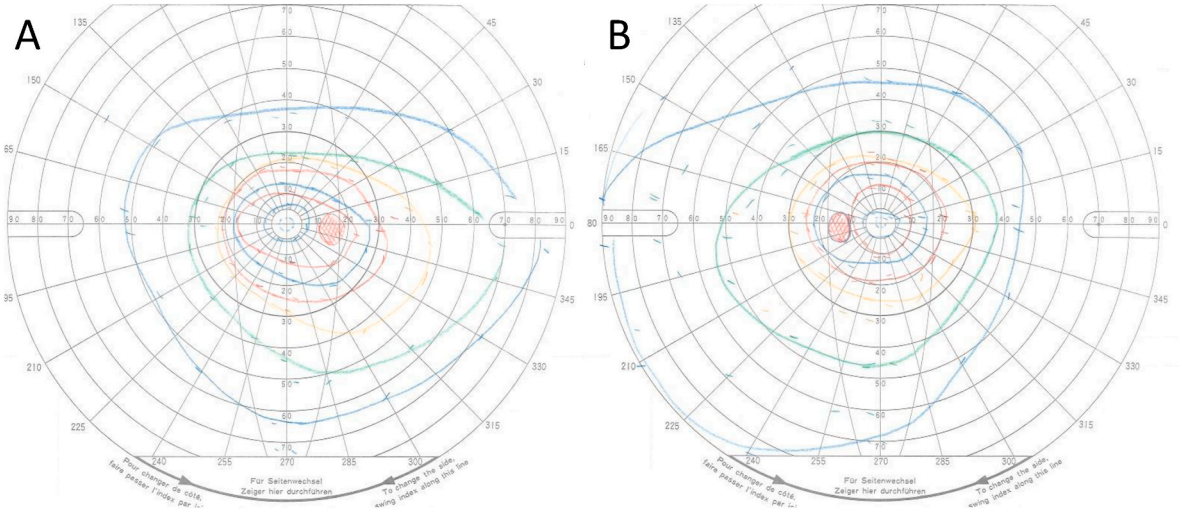

Fig. 2. Results of Goldmann perimetry (GP). GP demonstrating that there are no abnormalities in both eyes. (A: right eye, B: left eye) The isopters are as follow: (from the outermost blue line to the inner lines) V4e, III4e, II4e, I4e, I3e, I2e, I1e.

electroretinogram (ERG) (contact lens electrodes carrying light-emitting diodes; Mayo, Nagoya, Japan) revealed a loss of rod responses and significant attenuation of the cone responses in both eyes (Fig. 3). Detailed analysis of the posterior part of the fundus using multifocal electroretinogram (mfERG) (VERIS; Mayo, Aichi, Japan) showed there were poor responses in all examined fields, specifically in the nasal macular area of the left eye (Fig. 4). SD-OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA) showed that there was an obscured IZ that corresponded to the attenuated cone response of the ERG, while the RPE, ellipsoid zone (EZ) and external limiting membrane (ELM) were still preserved (Fig. 5). In order to try and correct the ornithine accumulation using a dietary reduction of its precursor arginine, the patient's parents were given nutritional guidance on how to avoid high arginine containing foods such as soybeans, nutmeat and meat. However, after these initial visits, he was not seen at our hospital for about 9 years. When he did return to our department for a subsequent visit at the age of 22, progression of posterior subcapsular cataract was seen. This resulted in slightly poor visualization of the posterior pole on OPTOS (Fig. 6). Although scalloped areas of chorioretinal degeneration had fused and were approaching the posterior pole, the fundus surrounding the disc and inside the posterior pole appeared to be intact on OPTOS (Fig. 6). However, SS-OCT (DRI OCT-1 Triton; Topcon Corp, Tokyo, Japan) showed that there was expansion of the region of the obscured IZ. In addition, the EZ and ELM adjacent to the region of the obscured IZ was also seen (Fig. 6).

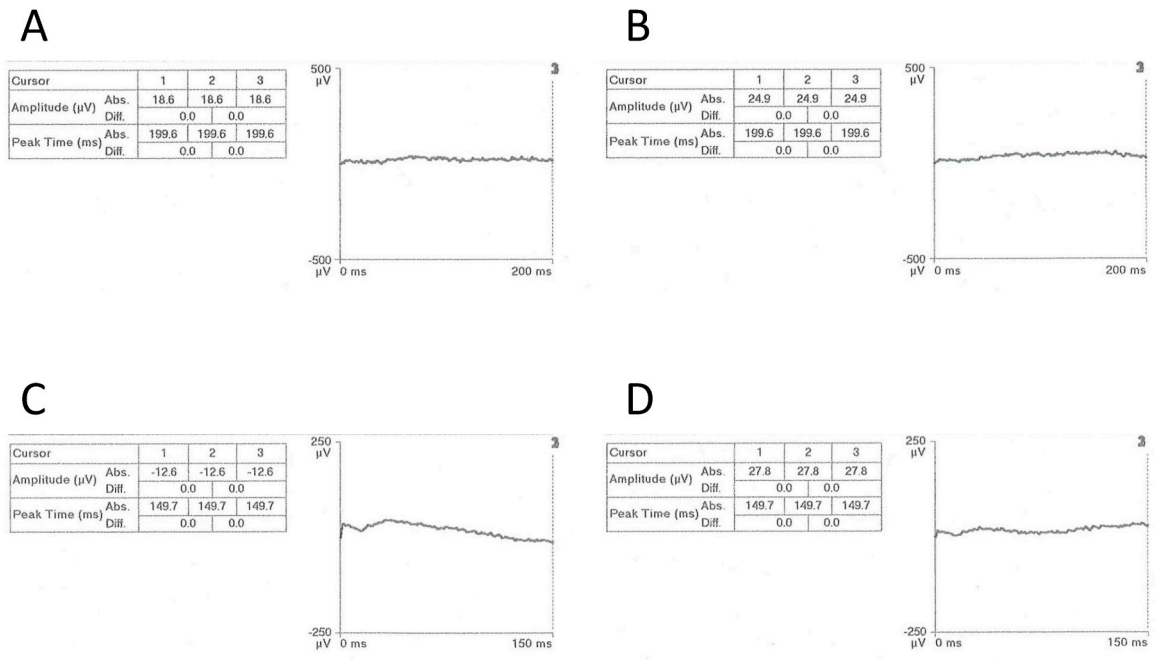

Fig. 3. Results of the electroretinogram (ERG). ERG revealing loss of the rod responses (A, B) and significant attenuation of the cone responses (C, D) in both eyes. (A, C: right eye, B, D: left eye).

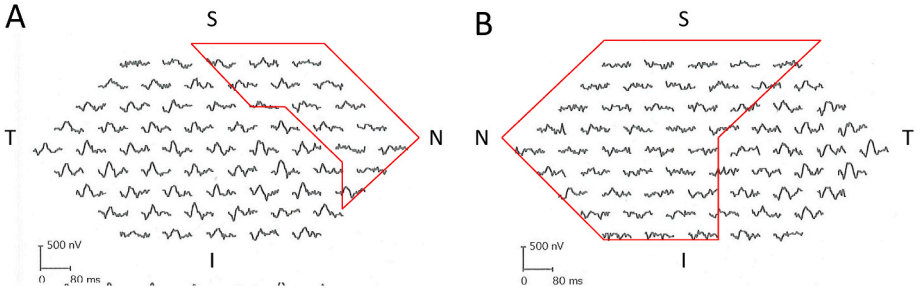

Fig. 4. Results of multifocal electroretinogram (mfERG). The array of signals (A, B) from both eyes recorded by mfERG. The areas surrounded by red frames show prominent depression. T = temporal. N = nasal. S = superior. I = inferior.

3. Discussion

In 1973, Simell and Takki were the first to report the findings that hyperornithinemia was associated with GA.[4] GA is a progressive chorioretinal degenerative disease associated to high levels of serum and urine ornithine due to a deficiency of OAT, which is inherited in an autosomal recessive manner.[1] Based on a fundus photography evaluation, Takki et al. proposed there were 4 stages of GA that depend on the area of the chorioretinal atrophy.[3,5] Briefly, they defined stage I as peripheral fundus atrophy only, stage II as peripheral fundus atrophy advancing toward the posterior pole with initial degeneration around the disc, stage III as apparent atrophy around the disc and stage IV as whole posterior pole atrophy except for the macula. Using OCT, it is possible to observe cystoid macular edema[6,7] or foveal IZ, EZ, ELM line interruption[8] of the GA. However, these previous reports were primarily for the late stages (i.e., stages III or IV) of GA, at which point the disease has already reached the disc or inside of the posterior pole.[3]

Wang et al. created an OAT-deficient GA mouse model. An ultramicroscopic study of knockout mice revealed that RPE abnormalities with normal photoreceptors were detected during the earliest stage in the GA model. Subsequently, focal degeneration and malfunction of the RPE cells appeared to lead to photoreceptor abnormalities and secondary atrophy of the choriocapillaris. These authors additionally found that an arginine-restricted diet substantially reduced the plasma ornithine levels and completely prevented retinal degeneration in this GA mouse model.[2,9] Furthermore, intravitreous injections of the ornithine solution in both rats and monkeys caused marked changes initially in the RPE that were subsequently followed by the gradual degeneration of the retina. At one hour following the injection, the RPE became diffusely edematous. Although the swelling of the RPE returned to a normal appearance at 24 h after the injection, electron microscopy revealed that many of the RPE cells were undergoing degeneration. In addition, the lamellar membranes of the photoreceptor outer segments had also lost their normal alignments.[10] This finding demonstrated that the disturbance that originated in the RPE initially influenced the outer portion of the photoreceptors, which may have caused the obscurity of the IZ that was observed by the OCT.

In contrast, although the ERG has been reported to show a decrease in the amplitude for both the rod and cone cell responses during the early stage of GA, ophthalmic findings of retinochoroidal atrophy at the posterior pole are not observed until the advanced stage.[11] In our current report, we present details on a patient (stage II) with obscured IZ that could be observed by OCT. It is thought that the IZ consists of the contact cylinders that are formed by the apices of the RPE cells that encase part of the outer segments of the cones.[12] That is, the obscured IZ could represent the changed structure of the cone that coincides with the

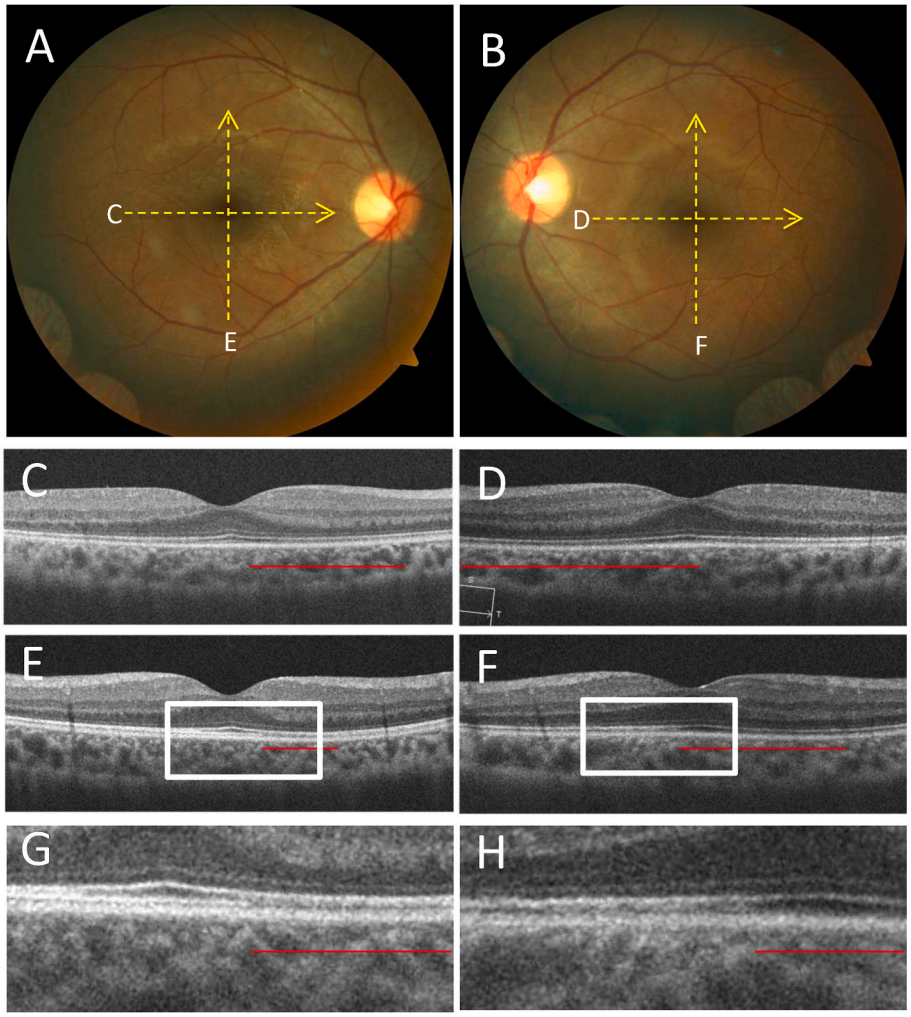

Fig. 5. Fundus photographs (FP) and SD-OCT. FP of right (A) and left (B) are shown. Dotted yellow arrows superimposed on FP indicate the direction of the SD-OCT images. SD-OCT images of the horizontal (C, D) and vertical (E, F) slice with red lines indicating the region where IZ is obscured. (G) is the magnified image of the white box in (E). (H) is the magnified image of the white box in (F). Images of the left eye (B, D, F, H) show a wider area of the obscured IZ as compared to that for the right eye (A, C, E, G).

diminished cone response that is seen when using ERG. A report of the focal macular ERGs after fovea-off rhegmatogenous retinal detachment (RRD) by Kominami et al. showed that a restoration of the EZ alone was not enough to improve the focal macular ERGs after fovea-off RRD. In addition, restoration of the EZ accompanied by that of the IZ was essential for the recovery of the focal macular ERGs.[13] These results indicate the importance of the integrity of the IZ for focal macular ERGs and, as seen in our current case, the disrupted IZ alone was enough to decrease the response of the VERIS.

When evaluating the IZ, it is important to recognize the phenomenon of normal IZ loss as an artifact due to the relative decentration of the OCT light and the pupillary central axis. Park et al. reported finding reduced reflectivity of the IZ due to the tilted OCT image when using the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) and that the hyper-reflective Henle fiber layer is a telltale sign.[14] Meanwhile, Otani et al. showed by intentionally tilting the OCT image to visualize the Henle fiber layer when using the same spectral domain OCT device as ours, their OCT image could visualize the IZ in both the hyper-reflective Henle layer side and the opposite side.[15] This discrepancy indicates that this phenomenon might be affected by the apparatus. Although our case only showed slight hyper-reflectivity in the Henle fiber layer, it appeared to be milder than that observed in Otani's OCT image, thereby indicating the effect of this phenomenon was small in our current case.

Our examination of the patient at 9 years after his initial visit revealed that there was a worsening of the IZ destruction, especially in the parafoveal zone, with the adjacent EZ and ELM becoming obscured. This disease progression supports the speculation that the IZ was initially damaged, after which there was subsequent damage to the EZ or ELM.

Our current case report is clinically significant with regard to understanding the early changes of GA, as we detected the obscured IZ in the absence of any RPE atrophy during multimodal imaging when using OCT, FAF and ophthalmic findings. The limitation is that since this is a single case report, more cases are needed to reach a conclusion.

4. Conclusion

An obscured IZ was confirmed during the early stage of GA in a teenage patient with a chief complaint of blurred vision. OCT is useful in the detection of minute morphological changes that have occurred earlier in GA.

Patient consent

Consent to publish this case report has been obtained from the patient and his father in writing.

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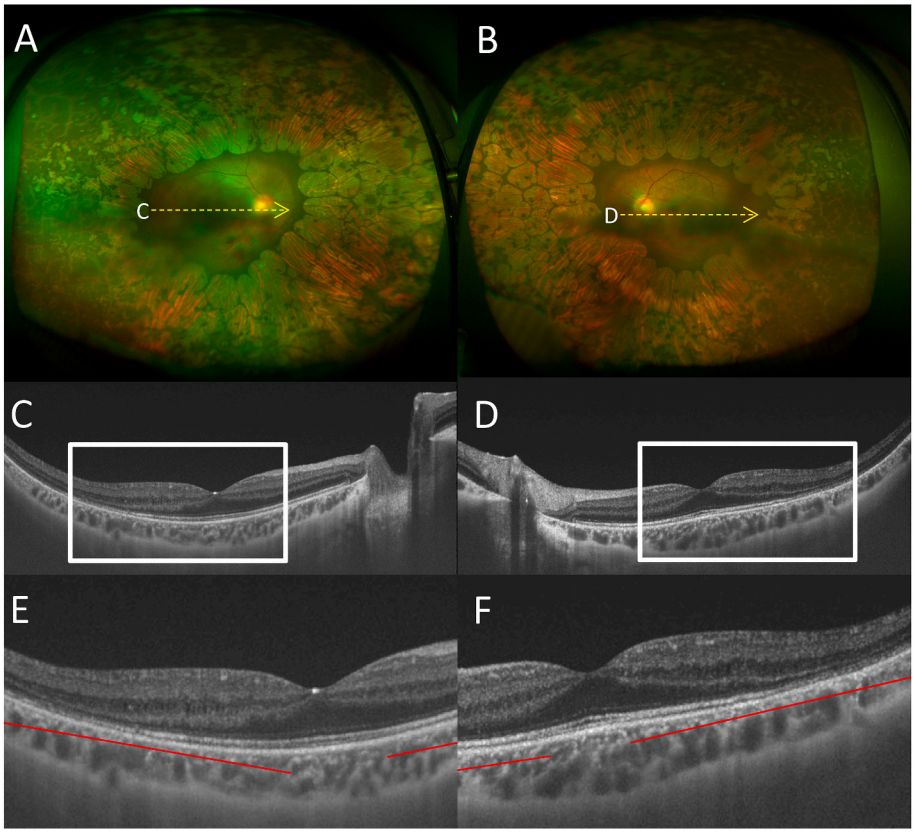

Fig. 6. Ultra-widefield fundus photographs (OPTOS) and SS-OCT obtained at age 22. OPTOS of right (A) and left (B) eye are shown. Scalloped areas of chorioretinal degeneration have fused and are approaching the posterior pole. Although it is difficult to clearly visualize the posterior pole due to the posterior subcapsular cataract, the foveal region appears to be intact. The dotted yellow arrows that are superimposed on the OPTOS indicate the direction of the SS-OCT images. SS-OCT images of the horizontal slice are shown in (C, D). (E) is a magnified image of the white box in (C). (F) is a magnified image of the white box in (D). Red lines in (E, F) indicate the region where the IZ is obscured. When compared to the image observed at the initial visit at age 13, the obscured region has expanded, which indicates that the IZ destruction has worsened. The adjacent EZ and ELM have also been obscured, especially in the temporal region of the fovea.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare no conflicts of interest, financial or otherwise.

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