Meaning of Visualizing Retinal Cone Mosaic on Adaptive Optics Images

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• PURPOSE: To explore the anatomic correlation of the retinal cone mosaic on adaptive optics images.

• DESIGN: Retrospective nonconsecutive observational case series.

• METHODS: A retrospective review of the multimodal imaging charts of 6 patients with focal alteration of the cone mosaic on adaptive optics was performed. Retinal diseases included acute posterior multifocal placoid pigment epitheliopathy (n = 1), hydroxychloroquine retinopathy (n = 1), and macular telangiectasia type 2 (n = 4). High-resolution retinal images were obtained using a flood-illumination adaptive optics camera. Images were recorded using standard imaging modalities: color and red-free fundus camera photography; infrared reflectance scanning laser ophthalmoscopy, fluorescein angiography, indocyanine green angiography, and spectral-domain optical coherence tomography (OCT) images.

• RESULTS: On OCT, in the marginal zone of the lesions, a disappearance of the interdigitation zone was observed, while the ellipsoid zone was preserved. Image recording demonstrated that such attenuation of the interdigitation zone co-localized with the disappearance of the cone mosaic on adaptive optics images. In 1 case, the restoration of the interdigitation zone paralleled that of the cone mosaic after a 2-month follow-up.

• CONCLUSION: Our results suggest that the interdigitation zone could contribute substantially to the reflectance of the cone photoreceptor mosaic. The absence of cones on adaptive optics images does not necessarily mean photoreceptor cell death. (Am J Ophthalmol 2014;■:■–■. © 2014 by Elsevier Inc. All rights reserved.)

ADAPTIVE OPTICS IS A NEW IMAGING MODALITY allowing visualization of the cone mosaic. However, the subcellular structure of cone photoreceptors at the origin of their reflectance on adaptive optics images remains uncertain. The aim of this study was to improve our understanding of the origin of the hyperreflective signal leading to the cone mosaic pattern on adaptive optics images. For this purpose, we retrospectively analyzed the multimodal imaging data of 6 cases of 3 different diseases affecting the outer retina.

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PATIENTS AND METHODS

• PATIENTS: The charts of 6 patients who had been examined between October 2013 and January 2014 were retrospectively reviewed. One patient had acute posterior multifocal placoid pigment epitheliopathy (APMPPE), 1 patient had hydroxychloroquine retinopathy, and 4 patients had macular telangiectasia type 2. All patients underwent multimodal imaging in addition to the routine examination.

This institutional clinical study was registered on clinicaltrials.gov (NCT01546181) and the procedures conformed to the tenets of the Declaration of Helsinki. Approval of the Ethics Committee of Saint-Antoine Hospital (Paris, France) was obtained.

• PROCEDURES: All patients underwent a comprehensive ophthalmologic examination, including the measurement of the best-corrected visual acuity (BCVA); dilated funduscopic examination; color and red-free fundus camera photography; infrared reflectance scanning laser ophthalmoscopy (SLO) and optical coherence tomography (OCT) imaging (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). Fluorescein angiography (FA) and indocyanine green angiography (ICGA) were performed when necessary at the treating clinician's discretion. In addition, adaptive optics images were obtained using a commercially available flood-illumination adaptive optics camera (rtx 1; Imagine Eyes, France). Retinal images were obtained in a 20 degree horizontal and 12 degree vertical field. Adaptive optics images were assembled in a montage and overlaid on the fundus photographs and the fundus projection of OCT images using i2k (DualAlign LLC, Clifton Park, New York, USA), GIMP v2.8.10, www.gimp.org, and Powerpoint (Microsoft, Seattle, Washington, USA).

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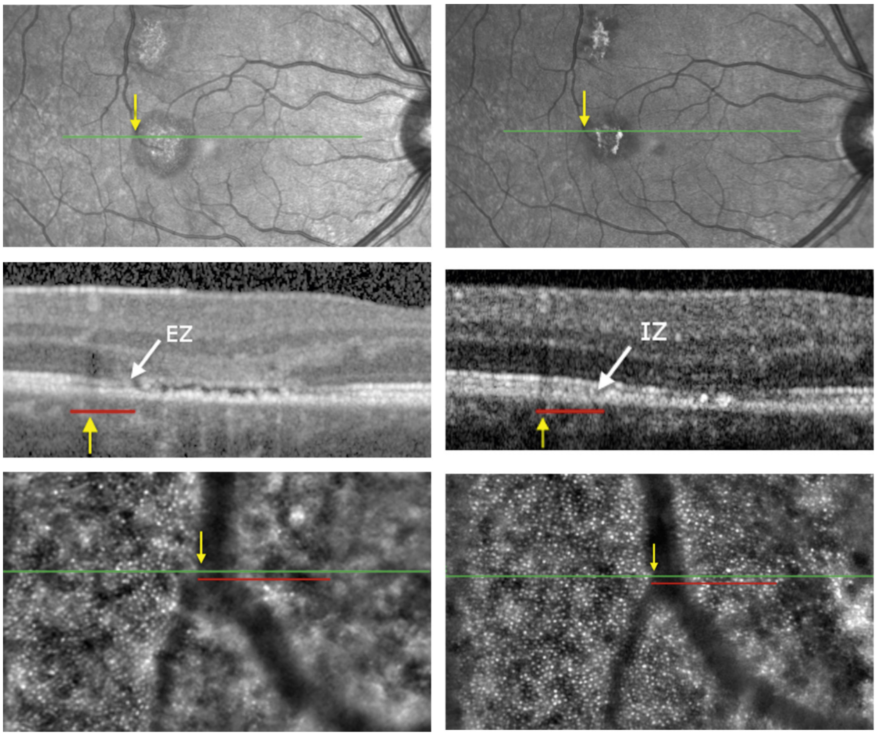

FIGURE 1. Acute posterior multifocal placoid pigment epitheliopathy at onset and after 2 months on adaptive optics images. (Top left) Infrared reflectance scanning laser ophthalmoscopy (SLO) fundus image of a 35-year-old man with acute posterior multifocal placoid pigment epitheliopathy 3 days after onset, showing 2 plaques in the macula of his right eye. An annular dark zone surrounds the center of the plaque. The green line indicates the position of the optical coherence tomography (OCT) B-scan. The yellow arrow shows the temporal edge of the plaque. (Top right) Infrared reflectance SLO fundus image after a 2-month follow-up. The scar is smaller than the initial plaque. (Middle left) OCT B-scan passing through the lesion shows the focal absence of the interdigitation zone, elevation and attenuation of the ellipsoid layer, and strong hyperreflectivity in the outer nuclear layer. The yellow arrow indicates the vessel on the temporal edge of the plaque where the interdigitation zone (IZ) has disappeared nasal to the vessel, although the ellipsoid zone (EZ) is still present. The red line indicates the distance on which the EZ is still present without IZ. The vessel is located at 5.4 degrees temporal to the foveal center. (Middle right) OCT B-scan passing through the plaque 2 months after onset shows a restoration of the IZ in the area where it was initially absent (red line). (Bottom left) Adaptive optics image of the superotemporal edge of the plaque. The green line indicates the position of the OCT scan. The yellow arrow indicates the vessel on the temporal edge of the plaque where the cone mosaic is absent nasal to the vessel, corresponding to the zone where the IZ has disappeared on OCT. The red line indicates the zone where the cone mosaic is absent at the edge of the plaque. (Bottom right) Adaptive optics image of the superotemporal edge of the plaque at 2 months showing restoration of the cone mosaic (red line) nasal to the vessel (yellow arrow), corresponding to the zone with restoration of the normal outer retinal architecture on OCT.

RESULTS

• **PATIENT 1:** A 35-year-old man with bilateral blurred vision, redness, and photophobia for 7 days and a history of viral syndrome 2 weeks prior was diagnosed with bilateral APMPPE. Baseline BCVA was 20/20.

Multimodal imaging of the paracentral lesion in the right eye showed a yellowish-white lesion on color photographs, early hypofluorescence and late staining on FA, hypo-autofluorescence on fundus autofluorescence, and hypofluorescence at the early and late phase of ICGA. On OCT, the outer retina was severely affected at the lesion center. Both the ellipsoid and the interdigitation zones had disappeared.[1] Adaptive optics imaging showed a central zone of coarse, hyperreflective spots. On the edge of the lesion, the ellipsoid zone was slightly attenuated, while the interdigitation zone was absent. This surrounding zone co-localized with a circular dark annulus devoid of cone mosaic on adaptive optics images. A normal cone mosaic was observed outside of the lesion.

After a 2-month follow-up, the lesion appeared smaller and, on adaptive optics images, its center was atrophic and contained highly hyperreflective structures. The latter co-localized with hyperreflective deposits in or on the retinal pigment epithelium (RPE) layer on OCT. The edge of the lesion (ie, the previously dark annulus) showed a normal cone mosaic structure on adaptive optics images, with restoration of the interdigitation zone on OCT (Figure 1).

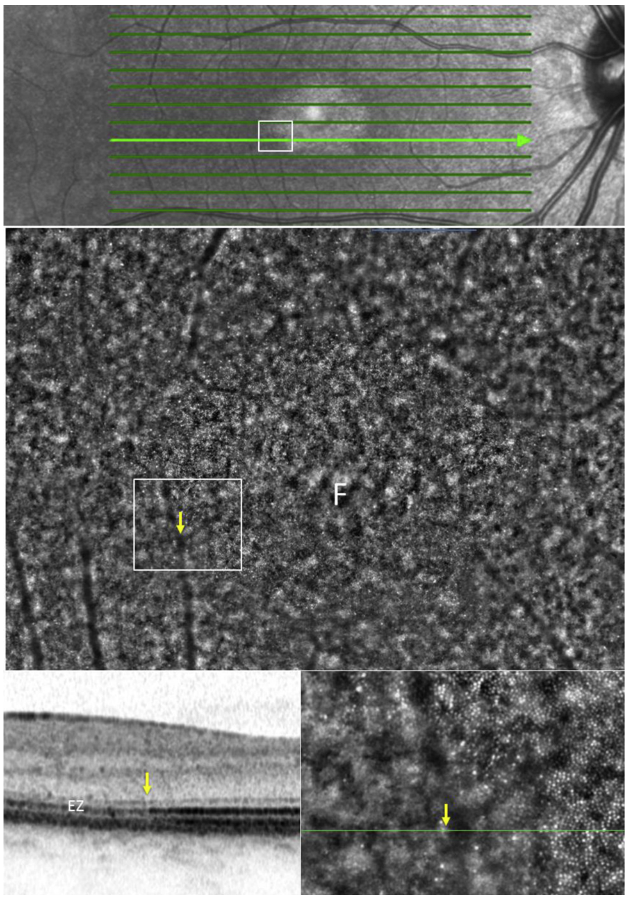

FIGURE 2. Hydroxychloroquine retinopathy on adaptive optics images. (Top) Infrared reflectance scanning laser ophthalmoscopy (SLO) fundus image of the right eye of a 45-year-old woman with hydroxychloroquine retinopathy. The central macula is still spared and appears brighter than the surrounding retina. The green line indicates the position of the optical coherence tomography (OCT) B-scan. The white rectangle indicates the zone shown on the bottom right image. (Middle) Adaptive optics image showing an oval area surrounding the foveal center (F) in which the cone mosaic is present. Outside of this area, the normal cone mosaic disappears on the adaptive optics image. The white rectangle, crossing the edge between the normal and abnormal retina, corresponds to the zone shown on the bottom right image. (Bottom left) OCT B-scan in the inferior temporal part of the macular region. Centrally to the yellow arrow, a normal outer retinal architecture is visible. Temporal to the arrow, a marked attenuation of the interdigitation zone is observed. The ellipsoid zone (EZ) is attenuated but still present. This zone corresponds to that where the cone mosaic disappears on adaptive optics image and is located temporal to the yellow arrow on the bottom right adaptive optics image. This transition zone is located 2.1 degrees temporal to the foveal center. (Bottom right) Adaptive optics image of the inferior temporal part of the macular region. The yellow arrow indicates the transition between the normal cone mosaic structure at the foveal side and the disappearance of the cone mosaic temporal to the arrow. The green line indicates the position of the OCT B-scan. The absence of the cone mosaic on adaptive optics image seems related to the disappearance of the interdigitation zone but still presents an ellipsoid zone (EZ) on OCT.

• **PATIENT 2:** A 45-year-old woman with a history of hydroxychloroquine sulfate intake for 20 years, at a dose of 200 mg/d for 10 years and then 400 mg/d for the next 10 years, was referred for retinopathy screening. The BCVA was 20/20. The treatment was discontinued because of paracentral defects on the Humphrey visual field test.

Multimodal imaging showed a central hyperreflective area on the infrared image (IR) surrounded by a hyporeflective annular structure in both eyes. Fundus autofluorescence was normal. OCT showed normal outer retinal layers in the central zone, whereas in the surrounding zone corresponding to the hyporeflective annular structure on IR a strong attenuation of the interdigitation zone was clearly seen. The overlying ellipsoid layer was still present and only slightly attenuated.

The central foveal zone showed the preservation of the outer retinal layers. This phenomenon of foveal photoreceptor resistance to toxic effects has been previously described.[2]

Adaptive optics images of the central zone of the retina revealed a normal cone mosaic structure up to approximately 2 degrees from the center, which corresponded to a zone of normal outer retinal layers on OCT. An annular structure surrounding this central zone was detected at the limit between the normal and atrophic retina. On adaptive optics, the disappearance of the normal cone mosaic was progressively replaced by a blurred image with black and gray spots. This zone corresponded to the highly attenuated interdigitation zone on OCT, although the ellipsoid zone was still present (Figure 2).

• **PATIENTS 3, 4, 5, AND 6:** Four patients diagnosed with early-stage macular telangiectasia type 2 (MacTel2) were seen for annual follow-up as part of the MacTel natural history study.[3] The visual acuity ranged from 20/50 to 20/25. Red-free fundus camera photography showed a whitening of the temporal side of the macular area. Fundus autofluorescence showed a slightly increased fluorescence temporal to the fovea. OCT showed foveal and parafoveal cysts in the inner and outer retina with disruption of the interdigitation and ellipsoid zones and a normal retinal thickness. Figure 3 shows the left eye of 1 patient with a visual acuity at 20/25. Nasal to the fovea, a zone with disappearance of the interdigitation zone but intact ellipsoid zone was seen. Adaptive optics images showed the disappearance of the cone mosaic in this area.

Similar findings were observed in the 3 remaining patients, in whom the absence of cone mosaic on adaptive optics images corresponded to the disappearance of the interdigitation zone while the ellipsoid zone was still intact on OCT.

Overall, a focal absence or strong attenuation of the interdigitation zone was noted in all 6 patients on OCT images, which corresponded to an area in which the cone mosaic had disappeared on adaptive optics images. In all cases the ellipsoid zone was preserved in the corresponding areas. No abnormalities were present in the inner retina that could have led to a shadow on the outer retina.

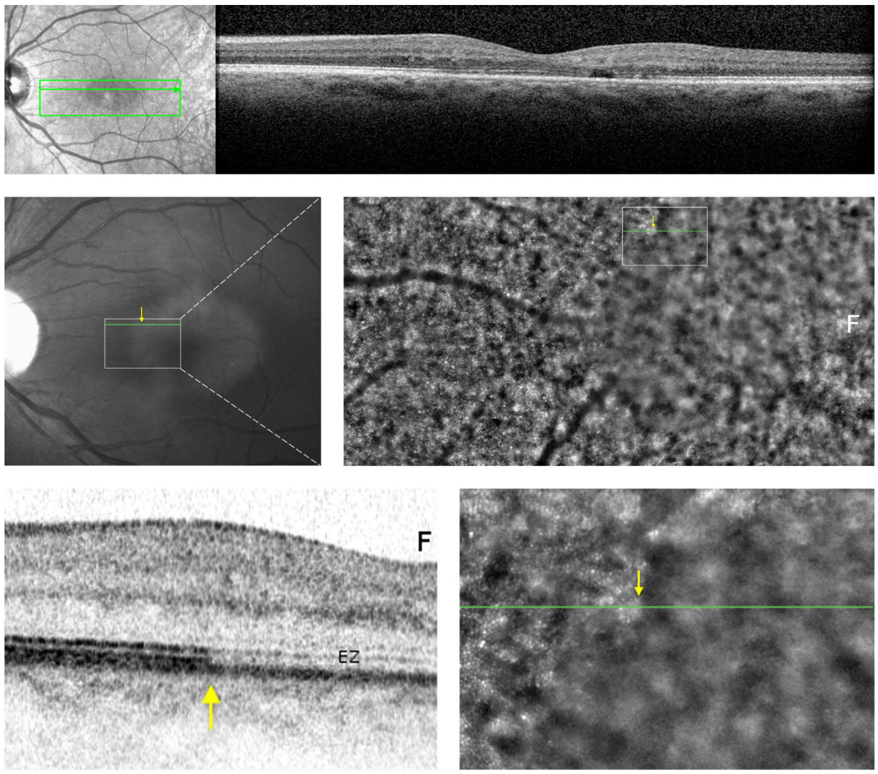

FIGURE 3. Macular telangiectasia type 2 on adaptive optics images. (Top left) Infrared reflectance scanning laser ophthalmoscopy (SLO) fundus image of the left eye of a 48-year-old man with an early stage of macular telangiectasia type 2. (Top right) Optical coherence tomography (OCT) B-scan at the green line seen on the infrared fundus image. An outer cavitation is present temporal to the fovea, but only minor anomalies are present nasally. (Middle left) Red-free fundus camera image shows the clear grayish oval zone typically observed in MacTel macula.[19] The white rectangle, crossing the limit between the normal retina and the MacTel zone (yellow arrow), indicates the zone displayed by adaptive optics. The green line indicates the position of the OCT B-scan shown below. (Middle right) Adaptive optics image showing a zone in which the normal cone mosaic has disappeared nasal to the foveal center (F). The white rectangle indicates the enlargement of the image shown below and the green line shows the position of the OCT B-scan. (Bottom left) OCT scan showing the disappearance of the interdigitation zone from the yellow arrow to the foveal edge (F), while the ellipsoid zone (EZ), although attenuated, is still present. (Bottom right) Adaptive optics image: the green line indicates the location of the OCT B-scan; the yellow arrow indicates the transition between the normal cone mosaic structure nasal to the arrow and the disappearance of the mosaic on the foveal side (F) of the arrow. This transition zone is located 2.3 degrees nasal to the foveal center (F). The absence of the cone mosaic on adaptive optics image seems related to the disappearance of the interdigitation zone but still presents an ellipsoid zone (EZ) on OCT.

DISCUSSION

IN THIS STUDY, THE CHARTS OF 6 PATIENTS WITH DIFFERENT retinal pathologies affecting the outer retina were retrospectively reviewed. They all had localized disruptions in the photoreceptor layers on OCT in areas located paracentral to the fovea, in which flood-illumination adaptive optics can provide a distinct visibility of the cone mosaic.[4]

We observed that the disappearance of the normal cone mosaic on the images of the macular area obtained with the adaptive optics fundus camera co-localized with a disruption of the interdigitation zone on OCT in all 6 cases, including areas in which the ellipsoid zone was still present. Conversely, a normalization of the normal cone mosaic in the case of APMPPE was observed during the follow-up and clearly showed the concomitant restoration of the interdigitation zone on OCT.

In the literature, several reports have discussed the origin of the high-reflectance signal of the cone mosaic on adaptive optics.

Most assumptions on the origin of the guided light reflected from cones invoke reflectance from 2 layers: the inner segment/outer segment junction (ellipsoid zone) and the terminal end of the outer segment. This has been supported by multiple research groups active in the field of optics.[5–10]

In parallel, Choi and associates[11] and Chen and associates[12] have reported that the loss of ellipsoid layer corresponded to areas devoid of cones in retinal dystrophies.

However, several more recent papers investigating adaptive optics images in different retinal diseases stated that the hyperreflective signals of cones shown by adaptive optics could originate from the interdigitation zone.

Kitaguchi and associates[13] have hypothesized that the interdigitation zone is more involved in the reflectance of the photoreceptor mosaic than the ellipsoid layer on adaptive optics images, based on their observations in 3 patients with macular microhole. Their main limitation was the poor visualization of the cone mosaic in the foveal area using adaptive optics systems. Two reports[14,15] on patients with acute zonal occult outer retinopathy have also found a correlation between an intact ellipsoid zone with disappearance of the interdigitation zone and the disappearance of the cone mosaic structure on adaptive optics images. They hypothesized that since cones were sparse while rods were intact in the affected zone, the rods could contribute to the intact signal of the ellipsoid zone. Other data (Miloudi C. et al, under revision in *Biomed Optics Express*, October 2014) have suggested that cones are the predominant contributors of the interdigitation zone while both rods and cones contribute to the ellipsoid zone based on their differential optical Stiles-Crawford effect. In addition, Ooto and associates[16,17] have reported that the interdigitation zone could play a more important role in the reflectance of the photoreceptor mosaic than suspected, based on their observations in resolved cases of central serous chorioretinopathy and in patients with surgically closed macular hole.

Our cases suggest that the alteration of the interdigitation zone seen on OCT could cause the disappearance of the cone mosaic seen on adaptive optics images. This assumption was confirmed in 1 case with the simultaneous restoration of the cone mosaic and of the interdigitation zone during recovery. We therefore agree with the aforementioned authors[13–17] that the interdigitation zone could contribute more to the reflectance of the photoreceptor mosaic than the ellipsoid zone on adaptive optics images. We think our cases are of additional value, as they describe different retinal diseases and 1 case showed normalization during the follow-up. The disappearance of the interdigitation zone on OCT could be the earliest sign of the loss of the normal cone mosaic on adaptive optics. This hypothesis also supports the findings of a report using adaptive optics and OCT,[18] in which the normal cone mosaic was clearly detected in the interdigitation zone, where the tip of the cone photoreceptor outer segment interdigitates with microvilli from retinal pigment epithelial cells.

Our results suggest that the interdigitation zone could contribute substantially to the reflectance of the cone photoreceptor mosaic. The absence of cones on adaptive optics images does not necessarily mean photoreceptor cell death.

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Biosketch

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