As described in the first report by Oguchi, the intensity of the tapetal-like reflex varied depending on the direction of the observation light against the retina.[1,17] A similar finding was reported for patients with X-linked retinoschisis.[10] This is probably because the layer where the tapetal-like reflex originates has the properties of a plane mirror, viz., the angle of reflection equals the angle of incidence. If the incident angle is almost perpendicular to the retinal surface, strong tapetal-like reflex can be observed, but if it is not, the intensity of the reflex decreases.[17] Theses reflective materials can be either layered structures or particles or chemical materials embedded in the outer segment discs, which are well aligned structures parallel to the retinal surface. The Mizuo-Nakamura phenomenon can be explained by the disappearance of mirror-like reflective materials following prolonged dark-adaptation. The incident angle against the reflective materials, however, can be easily changed by the interfering retinal structures which have different refractive indices, such as a thickened vitreo-retinal interface or vessel walls of retinal arteries or thickened RNFL. Changes in the distribution patterns of the tapetal-like reflex in Figure 4 can be more easily explained by the modulation of outer retinal reflex due to the inner retinal structures than by the local functional changes of the photoreceptors or RPEs *per se*. The increased or decreased reflectivity of the tapetal-like reflex may be due to the refractive structures which change the incident angle of the observation light. For example, vitreous traction on the retina can change during the natural course of the disease process, and this may change the reflection of the vitreo-retinal interface, leading to the changes in distribution of the dark regions as observed in some of our cases (**Fig. 2**).

In addition, the direction and strength of the vitreoretinal traction may change during aging even before the posterior vitreous detachment is completed. This may explain the spontaneous changes in the distribution patterns of the dark regions in younger patients. The observations by OCT, however could not detect either non-homogeneous vitreous distribution or posterior hyaloid detachment locally along the border of the dark regions (**Fig.8**). The interfering materials which can decrease the tapetal-like reflex may be too small and thin to be detected by the current imaging techniques.

The decreased or increased reflectivity along arteries could be similarly explained (**Fig. 6**). Compared to the retinal veins, the retinal arteries are composed of additional muscle layers and appear more hyperreflective.[18] Light passing beside the retinal arteries may be refracted and change the reflectance from the outer retina, although part of dark regions along the artery look too large to be simply explained by this change (**Fig. 6C**).

The alterations of the dark and tapetal-like reflex regions can be explained by changes in the refractive modulations in the inner retina. However, we could not find any metallic reflex in the dark regions even though we examined the retina from different directions (data not shown). The border between regions with and without tapetal-like reflex was always clear irrespective of the viewing angle. There must be another mechanism which changes the retinal reflectivity in Oguchi's disease.

The tapetal-like reflex of the Mizuo-Nakamura phenomenon has been reported in other diseases such as X-linked cone-rod dystrophy,[19] X-linked retinoschisis,[10,20] and also in carriers of X-linked retinitis pigmentosa.[21] The underlying mechanism for this reflex has not been clearly determined by our case series, and the discussion we have made regarding possible mechanisms is very speculative. However, our results have given us important insights on the origin of this unusual fundus reflex.

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Figure legends

Figure 1. Fundus photographs of eyes with Oguchi's disease showing clearly demarcated dark regions. The dark regions without tapetal-like reflexes are located along or posterior to the equator (arrows) in Case 1 (**A and B**), Case 2 (**C and D**), Case 3 (**E**) and Case 11 (**F**).

Figure 2. Dark regions demarcated by retinal arteries. The locations of the retinal arteries are shown by white dots in the right columns. The dark regions are partially demarcated by retinal arteries but not by veins (arrows), in the right eye of Case 1 (**A**), the left eye of Case 1 (**B**), the left eye of Case 2 (**C**), and the left eye of Case 3 (**D**).

Figure 3. Optical coherence tomographic (OCT) image (**A**) and fundus autofluorescence (AF) image (**B**) of a case with clearly demarcated dark regions. Horizontal scan image was obtained for 9.0 mm in the superior-temporal portion of the right eye in Case 1 across the regions with and without tapetal-like reflex **(A, right**). The border between the dark region and the region with the tapetal-like reflex in the OCT image is indicated by an arrow. The reflectance of the photoreceptor layer is much

higher in the region with tapetal-like reflex than in the dark region. There are no apparent structural abnormalities in either the inner retinal layers or outer retinal layers or the choroid. In the AF image, there are no demarcated lesions corresponding to the dark regions in the fundus photograph (**B, asterisks**).

Figure 4. Expansion and contraction of the dark regions during the follow-up period. The area of the dark region is reduced and the tapetal-like reflex expanded during the 4 year and 5 months follow-up in the superior portion of the right eye of Case 1 (**A**). The dark region is reduced and absent during the 4 year and 7 months follow-up in the left eye of case 2 (**B**). The dark region expanded during 2 years and 2 months follow-up in the right eye of Case 3 (**C**). The regions with and without tapetal-like reflex interlaced, and the dark region either expanded or contracted during the follow-up period depending on the retinal locations in the right eye of Case 1 (**D**). Photographs of individual patients were aligned so that their vertical retinal locations matched the others. The borders between the dark regions and the regions with tapetal-like reflex at the different ages of examination are indicated by either white dots or black dots or asterisks.

Figure 5. Comparison of the borders of the dark regions during light-adaptation.

Prolonged dark-adaptation for 180 minutes reduced the area of the tapetal-like reflex (Mizuo-Nakamura phenomenon) in the right eye of Case 1 (**A, left**). After 20 minutes of light-adaptation, the tapetal-like reflex reappeared (**A, right**). In the magnified image of the superior retina (**B**), the dark region became clearly visible at the same location and its border did not change during the course of light-adaptation (**white arrows**).

DA; dark-adaptation, LA; light-adaptation. Arrows indicate the same retinal locations in the superior retina.

Figure 6. High and low reflective regions along the peripheral arteries.

(**A**) Highly reflective regions are observed along the retinal arteries (**arrowheads**) but not along the veins.

(**B**) Low reflective regions are observed along the retinal arteries (**arrowheads**) but not along the veins.

(**C**) Both high- and low-reflectivity regions are observed at the same location of the retinal artery in the left eye of Case 4 (**C, left**). The dark regions are observed along peripheral arteries, but located slightly apart from the vessels in the left eye (**C, middle**) and right eye (**C, right**) of Case 3.

A; artery, V; vein.

Figure 7. A dark region running along the retinal nerve fiber layer (RNFL) bundle can be seen in the nasal sector of the left eye of Case 4 (left). Prolonged dark-adaptation for 180 minutes reduced the tapetal-like reflex, and the border of dark region cannot be detected (middle). The dark region along the bundle of RNFL disappeared during the 3 years and 6 months of follow-up (right).

LA; light adaptation, DA; dark adaptation. Arrows indicate the same retinal locations in the nasal retina.

Figure 8. Optical coherence tomographic (OCT) images across the regions with and without tapetal-like reflex. High-contrast vitreous images were obtained by a swept-source OCT. Horizontal line scan images in the superior portion of the right (A) and left (B) eyes in Case 1 are presented. The vitreous appears homogeneously distributed over the dark regions, and a posterior vitreous detachment cannot be observed. There were no abnormalities in the vitreoretinal interface along the border of the dark regions (**arrows**).

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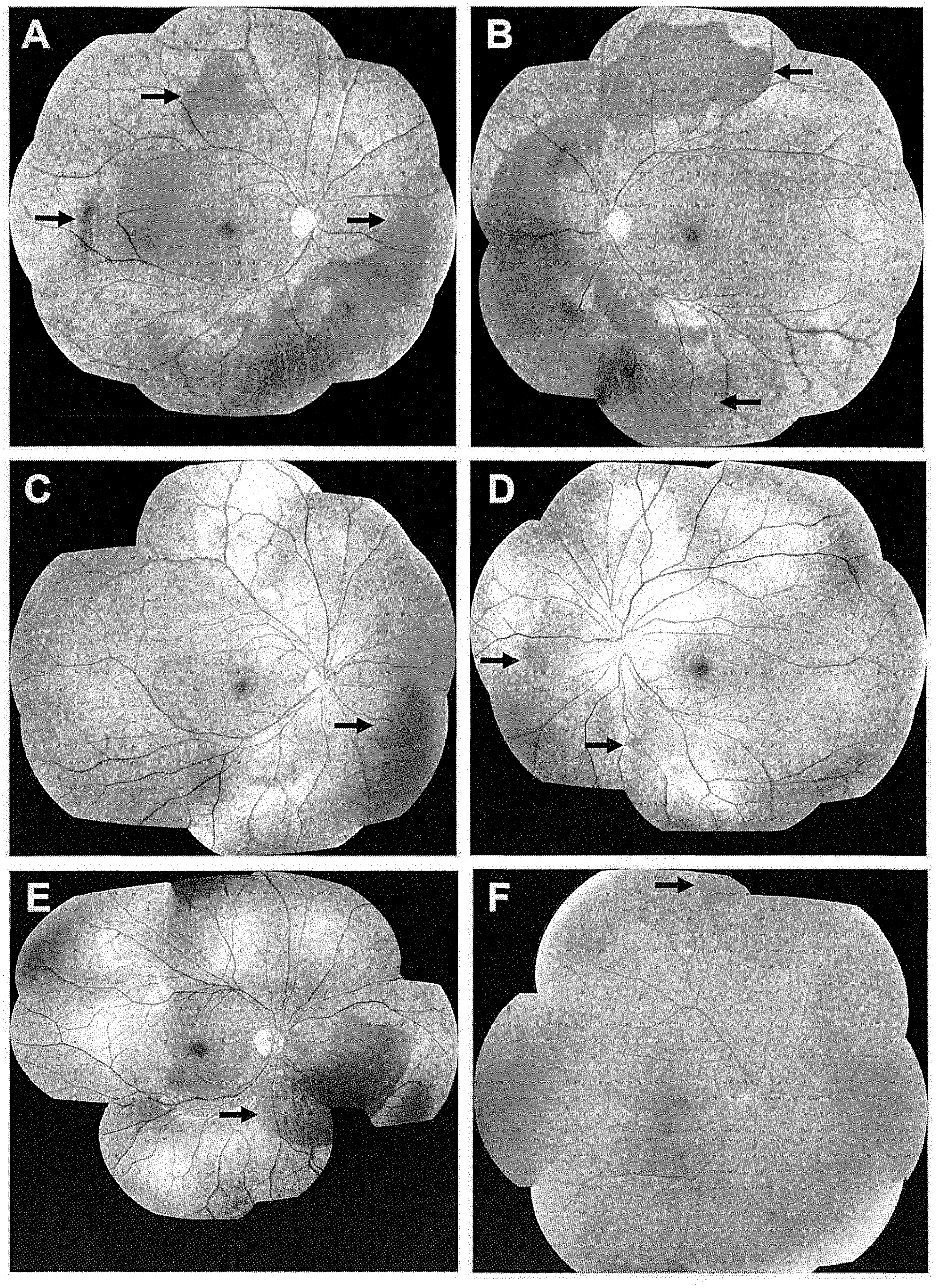
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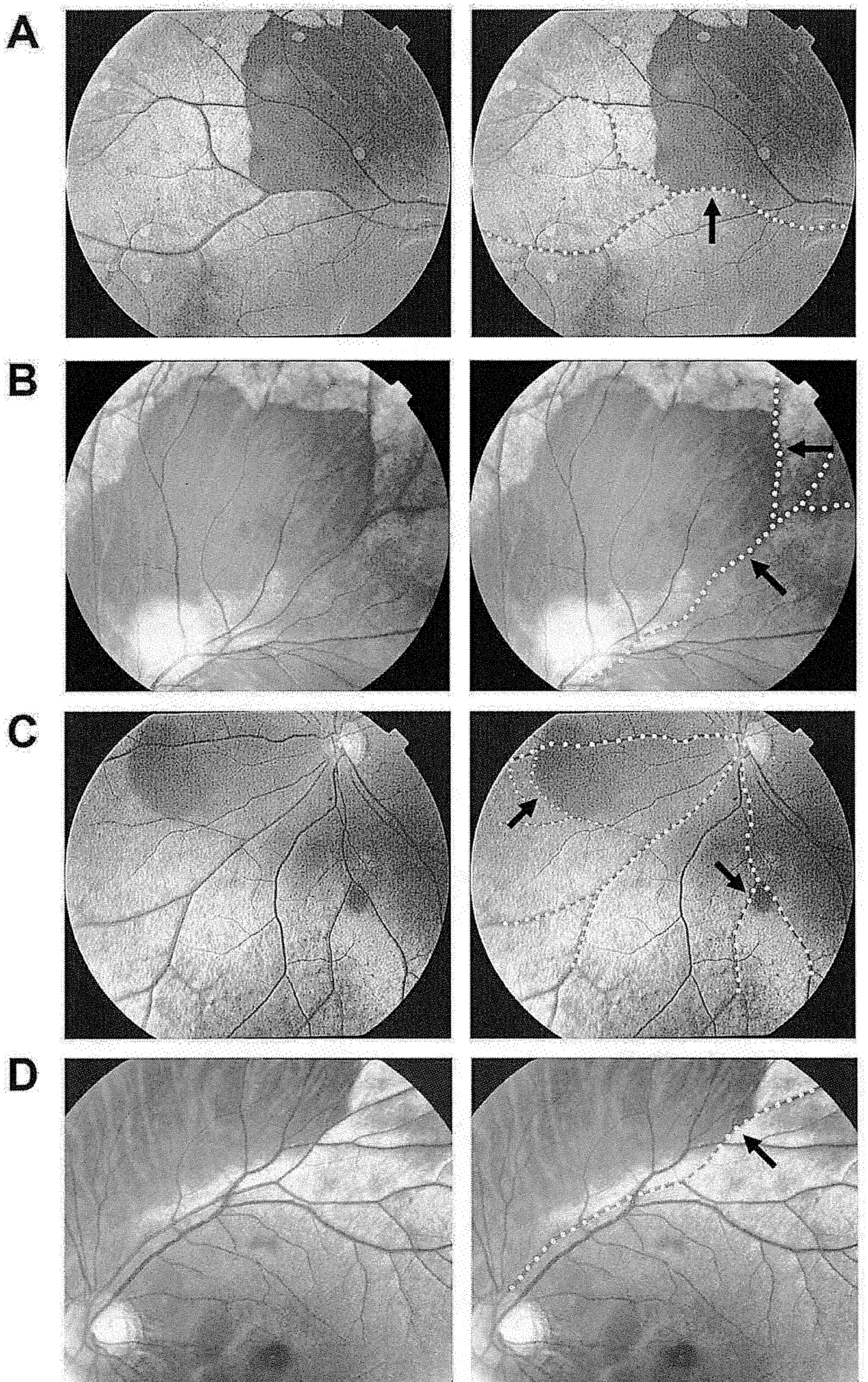
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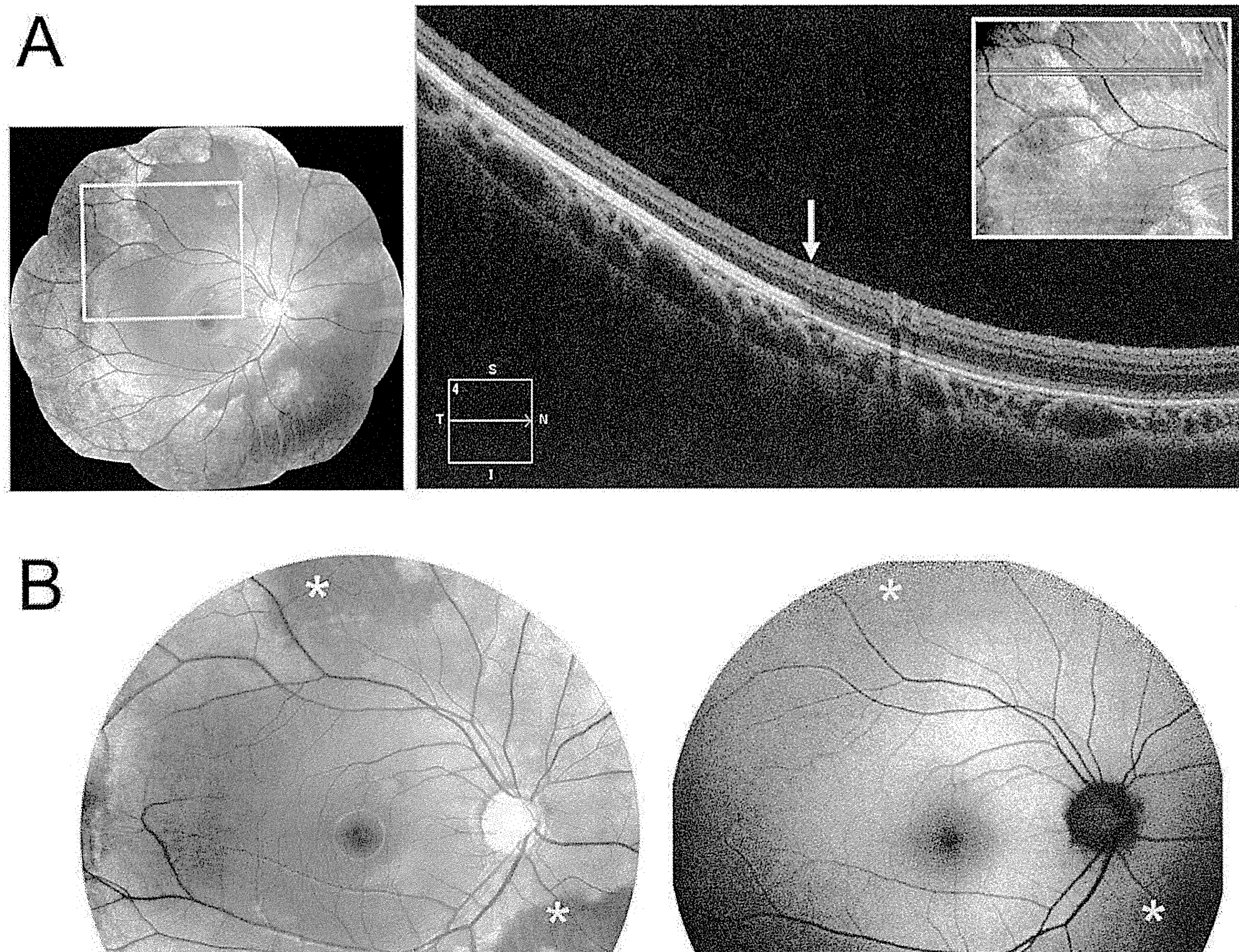
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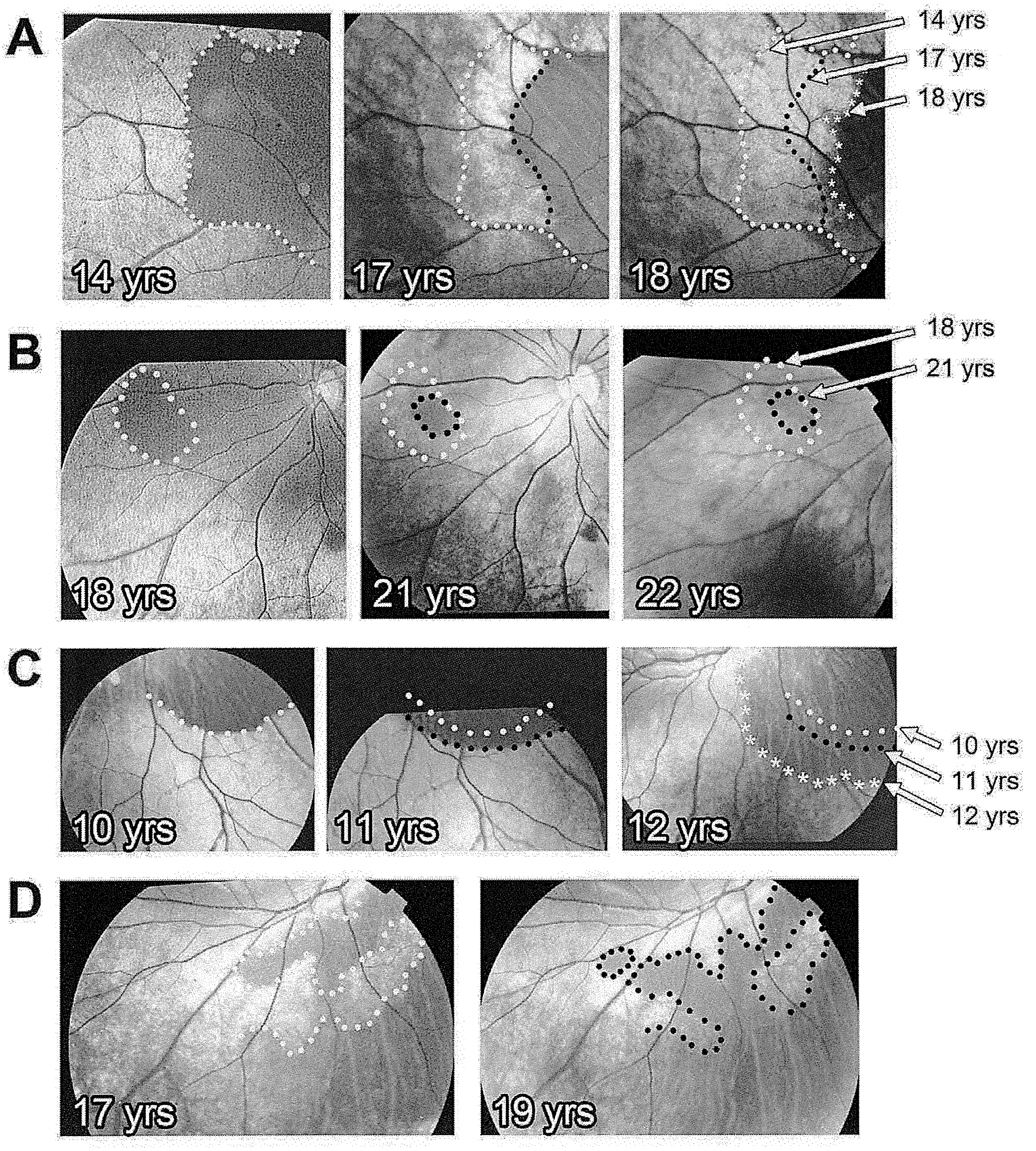

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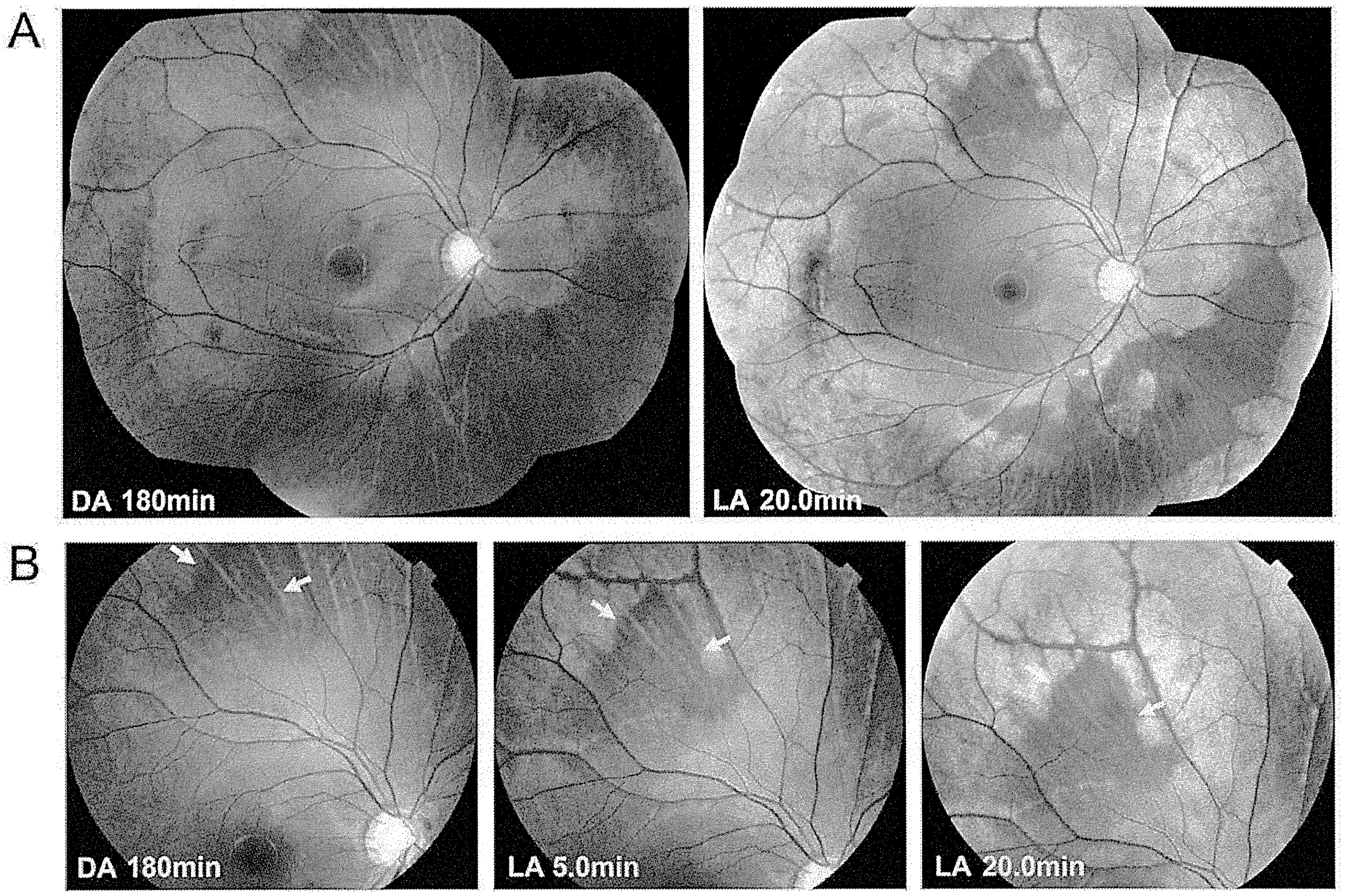
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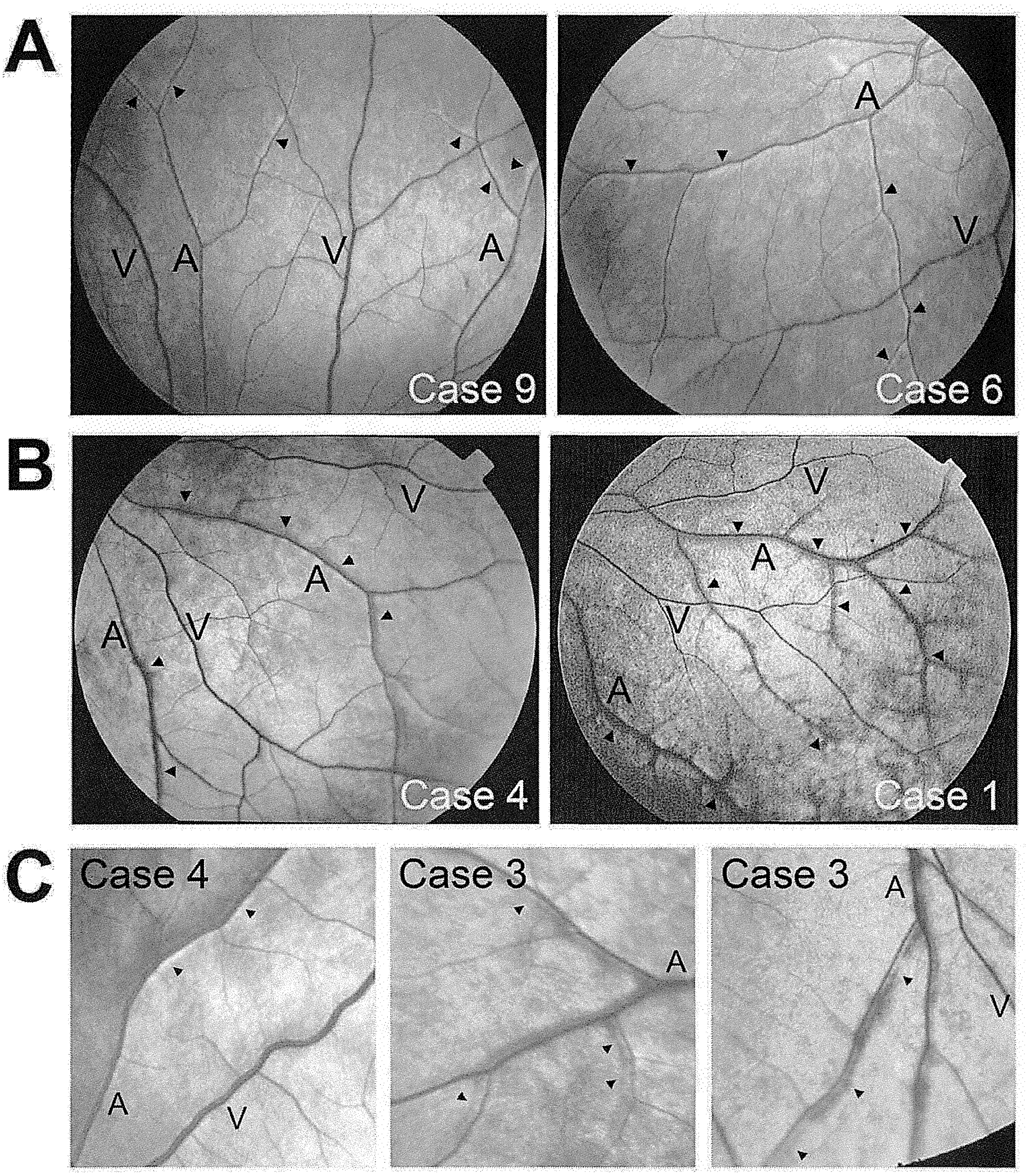
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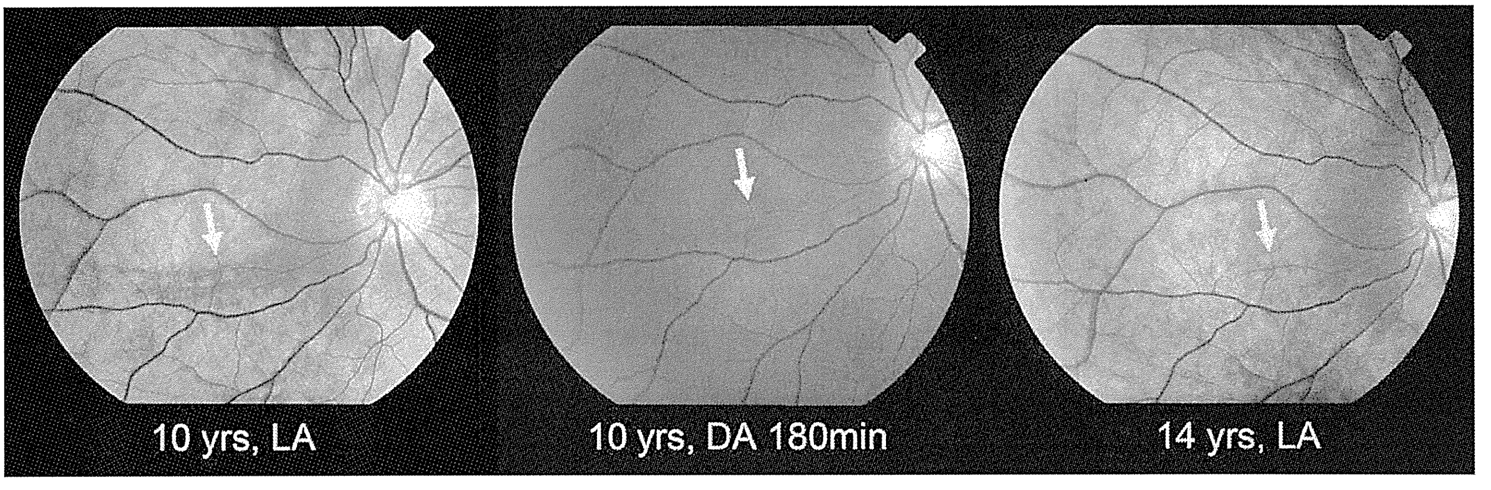
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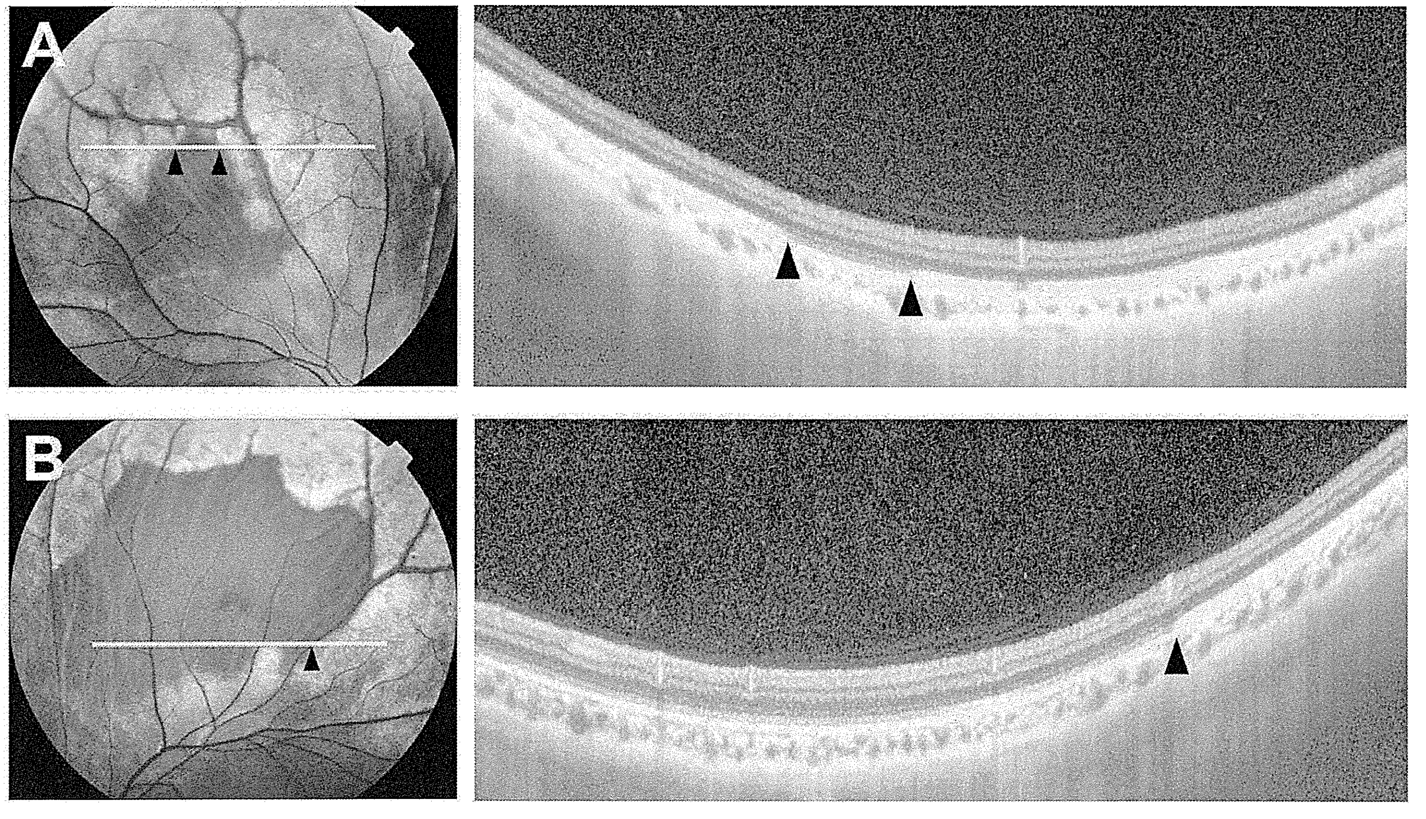
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