Retinal Pigment Epithelium Atrophy After Subretinal Voretigene Neparvovec-rzyl for RPE65-Related Disease: A 6-Month Follow-Up

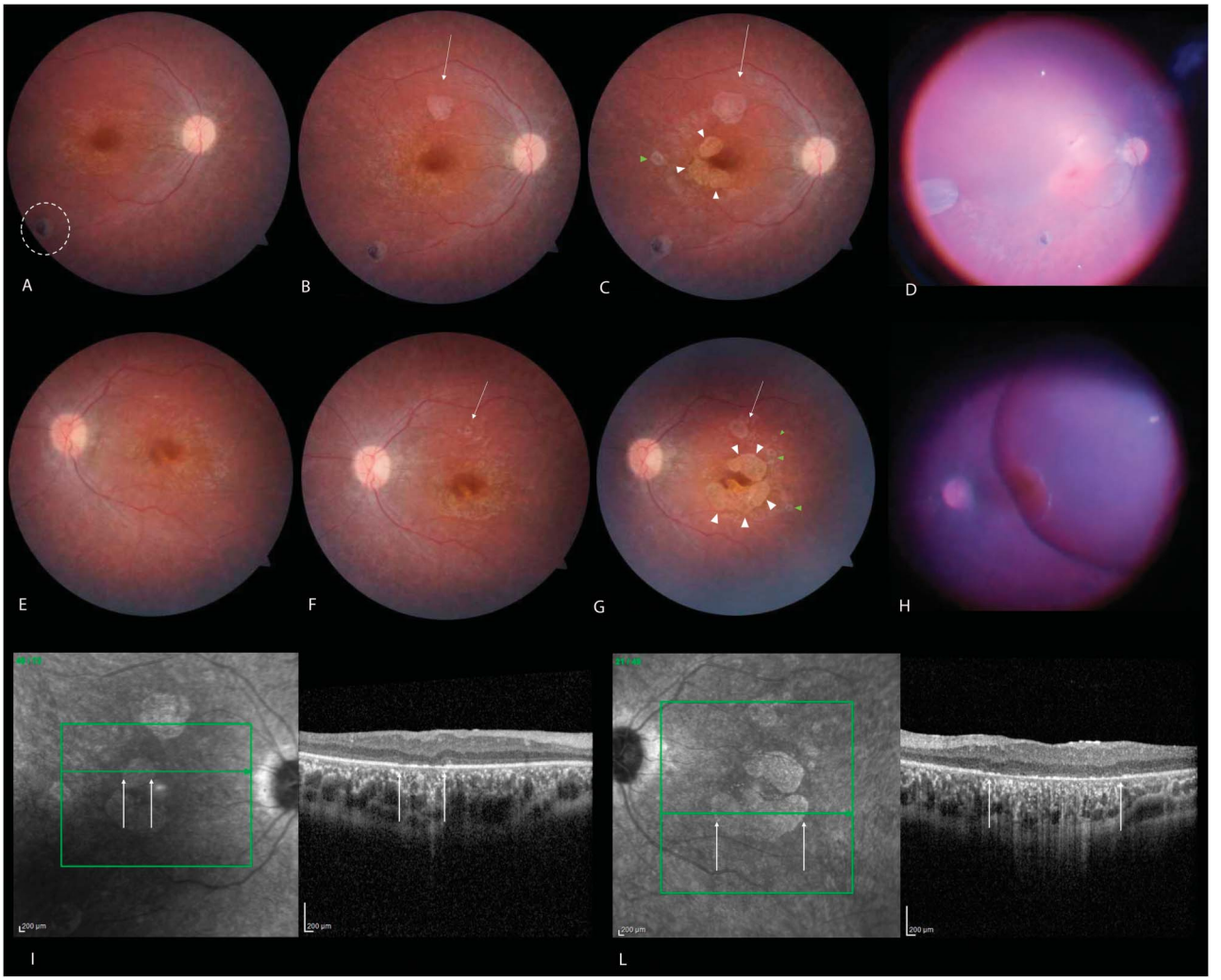

Fig. 1. Color fundus photographs of the right eye (**A**–**C**) and the left (**E**–**G**) eye of a 20-year-old male patient showing bilateral progressive RPE atrophy during a 6-month follow-up after VN gene therapy. Intraoperative images (**D** and **H**) demonstrating the extent of the subretinal bleb. Before the VN injection, a small atrophic area is present in the right eye (**A**) (white circle); 3 months after the VN injection, a small circular atrophic area appears at the posterior pole (**B**) (arrow) which corresponds to the touchdown site of the cannula for the subretinal injection; 6 months after the VN injection, 4 small RPE atrophic areas appear (arrowheads) (**C**): 3 small coalescent perifoveal areas (white arrowheads) and one small atrophic area at the boundaries of the vascular arcades (green arrowhead). In the left eye, image (**F**) showing a small RPE atrophic area 3 months later VN gene therapy (arrow) which corresponds to the touchdown site of the cannula, image (**G**) showing confluent perifoveal RPE atrophic areas (white arrowheads) and small circular atrophic RPE areas inside the vascular arcades (green arrowheads) 6 months later the VN gene therapy. Optical coherence tomography images (**I**, **L**) showing atrophic RPE areas (arrows) of the right and the left eyes, respectively.

Retinal disease caused by biallelic mutations in the *RPE65* gene is a sight-threatening disorder that eventually progresses to complete blindness.[1] Voretigene neparvovec (VN) gene therapy (Luxturna, Spark Therapeutics, Philadelphia, PA) is the current treatment for patients affected by retinal dystrophy caused

by biallelic *RPE65* mutations.[2,3] Some common adverse events were intraocular pressure elevations (18%), cataract (18%), retinal tears (8%), and ocular inflammation (8%).[2,4] To date, there is only one report which described the occurrence of chorioretinal atrophy after VN gene therapy in 18 eyes of 10 patients.[5]

We have reported a 6-month follow-up of a 20-year-old patient who developed a progressive bilateral retinal pigment epithelium atrophy (RPE) after subretinal injection of VN (Figure 1). Our findings agree with the results of Gange et al[5]; more specifically, we showed that even the atrophic areas which correspond to the touchdown site of the cannula for the subretinal injection enlarged up to 6 months of follow-up (Figure 1). Although the pathogenesis of the chorioretinal atrophy is not known at this time, Gange et al[5] hypothesized several potential factors which could be responsible of this phenomenon; moreover, Gange et al[5] observed the progressive enlargement in all patients up to the last follow-up examination, in 1 case up to 18 months. Regarding our patient, the areas of atrophy occurred on areas already devoid of photoreceptors before the treatment, sparing the center of the fovea; for this reason, we attributed the main cause of the development of these atrophic areas to the atrophy of the RPE. Furthermore, in our patient, we did not observe a worsening of the visual acuity (0.60 logMAR in both eyes) and visual field (Goldmann visual field); however, we did not know how this phenomenon will change over a longer period of time.

Key words: gene therapy, RPE65, atrophy, inherited retinal disease.

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