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RETINAL DISORDERS

Diabetic retinal pigment epitheliopathy: fundus autofluorescence and spectral-domain optical coherence tomography findings

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Abstract
Purpose To describe the characteristics of an unfamiliar disease entity, diabetic retinal pigment epitheliopathy (DRPE), using fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (SD-OCT).
Methods This retrospective study included 17 eyes from 10 proliferative diabetic retinopathy (PDR) patients with granular hypo-autofluorescence and/or variable hyper-autofluorescence on FAF (DRPE group) and 17 eyes from 10 age- and sex-matched PDR patients without abnormal autofluorescence (PDR group). Eyes with diabetic macular edema were excluded. Visual acuity (VA), retinal thickness (RT), and choroidal thickness (CT) were compared between the groups.
Results Eyes in the DRPE group had worse logMAR VA than eyes in the PDR group (0.369 ± 0.266 vs. 0.185 ± 0.119; $P = 0.026$). The thickness of the retinal pigment epithelium plus the inner segment/outer segment of the photoreceptors was reduced to a greater degree in the DRPE group than the PDR group ($P < 0.001$). Moreover, the thickness of the outer nuclear layer plus the outer plexiform layer was thinner in the DRPE group than in the PDR ($P = 0.013$). However, the thickness of the inner retina showed no differences between the two groups. CT was significantly thicker in the DRPE group than in the PDR group (329.00 ± 33.76 vs. 225.62 ± 37.47 μm; $P < 0.001$).
Conclusions Eyes with DRPE showed reduced VA, a thinner outer retina, and thicker choroid in comparison with eyes with PDR. Alterations of autofluorescence on FAF and changes in the outer retinal thickness and CT on SD-OCT can be helpful for differentiating DRPE in patients with PDR.

Keywords Diabetic retinal pigment epitheliopathy · Fundus autofluorescence · Proliferative diabetic retinopathy · Spectral-domain optical coherence tomography

Introduction

The retina has a dual blood supply, consisting of choroidal and retinal blood circulation. The choroidal blood circulation primarily supplies oxygen and nutrients to the outer retina, including the highly metabolic photoreceptors and retinal pigment epithelium (RPE); the retinal blood circulation supplies the inner retina. These two circulatory systems are completely segregated from the neural retina by the inner and outer blood-retina barrier (BRB) [1]. The inner BRB is formed by tight junctions between endothelial cells in the retinal vessels, and the outer BRB consists of tight junctions between RPE cells [2, 3]. Inner BRB breakdown in the retinal circulation is known to be a major cause of diabetic retinopathy (DR), which is the leading cause of blindness in working age groups [4, 5].

However, the significance of choroidal circulation and RPE cell dysfunction has been underestimated with regard to the progression of diabetic eye diseases. Some studies have reported choroidal vascular abnormalities, including obstruction and dilation of the choriocapillaris, choroidal neovascularization, and decreased choroidal blood flow in diabetic eyes, which were histopathologic characteristics of diabetic choroidopathy (DC) [6, 7]. Other studies have shown changes in RPE cells in diabetic patients, such as deepening hollows in

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the basal infoldings of the RPE cells and loss of occludin, which is a major component of the tight junctions in the outer BRB [8, 9]. Moreover, it was reported that diabetic macular edema (DME) with serous macular detachment showed hypo-autofluorescence in near-infrared autofluorescence imaging, which implied RPE dysfunction [10].

Fundus autofluorescence (FAF) is typically used to monitor lipofuscin accumulation, which provides indirect information about RPE metabolic activity [11, 12]. This functionality allows the use of FAF to evaluate abnormalities of the RPE in various retinal disorders such as age-related macular degeneration (AMD) and drug-related retinal toxicity. Furthermore, with the advent of spectral-domain optical coherence tomography (SD-OCT), the pathoanatomy of the retina can be evaluated non-invasively and conveniently. Choroidal thickness (CT) can also be measured using SD-OCT with the enhanced depth imaging (EDI) technique in normal and various pathologic states [13]. Changes in CT have been found in various retinal disorders, including central serous chorioretinopathy (CSC), AMD, polypoidal choroidal neovascularization (PCV), and DME [14].

In this report, we describe the characteristics of 17 eyes of 10 patients with proliferative diabetic retinopathy (PDR) who presented with abnormal RPE changes without any sign of DME, using FAF and SD-OCT.

Method

Patients

This retrospective comparative case series reviewed 259 patients with diabetic retinopathy who underwent fundus photography (FP), fluorescein angiography (FA), FAF, and SD-OCT at the Eye Center of Yonsei University Medical Center, Seoul, Korea, from January 2010 through December 2012. Seventeen eyes of 10 PDR patients with abnormal autofluorescence (AF) spots at the macula on FAF and 17 eyes of 10 age- and sex-matched PDR patients were included for statistical analysis. All eyes had been treated with panretinal photocoagulation (PRP) for PDR at least 12 months prior to inclusion in the study. Major exclusion criteria were the presence of other retinal diseases (e.g., AMD, PCV, chronic CSC, DME, or epiretinal membrane) and refractive errors of more than ± 3.0 diopters, which could influence retinal and choroidal thickness. Eyes with a history of ocular inflammation, ocular trauma, glaucoma, or focal or grid laser treatment were also excluded. In addition, eyes that had been treated by PRP within the prior 12 months were excluded, as PRP can affect CT and retinal thickness (RT) [14–17]. Eyes with macular non-perfusion and/or enlargement of the foveal avascular zone on FA were also excluded, because those findings may be associated with thinning of the inner retina and/or outer retinal changes [18].

Abnormal AF spots on FAF were defined as multiple granular hypo-AF and/or variable hyper-AF at the RPE level in the macula. No eye presented zonal areas of hypo-AF and/or hyper-AF or descending tracts on FAF, which would be signs of previous chronic subretinal fluid. Moreover, neither subretinal fluid nor cystoid macular edema was identified on SD-OCT in any of the patients. Changes in AF caused by intraretinal hemorrhage or hard exudates were not categorized as abnormal AF after comparing FP and FAF. Furthermore, eyes with drusen, which induces hyper-AF on FAF, were excluded from the study. The presence of an abnormal FAF was evaluated by two independent retina specialists (ECK and YS); any disagreement was settled by discussion with a senior investigator (SHB).

Two patterns of abnormal AF were noted in this study. Diffuse granular hypo-AF with variable hyper-AF in the macular area was seen in 12 eyes (Fig. 1b). Five eyes presented central granular hypo-AF surrounded by marginal focal hyper-AF in the macula (Fig. 1d).

Eyes with abnormal AF and age- and sex-matched eyes without abnormal AF were categorized into the diabetic retinal pigment epitheliopathy (DRPE) group and the PDR group, respectively. Representative cases of FAF in the two groups are shown in Fig. 2. Institutional review board approval was obtained, and the study adhered to the tenets of the Declaration of Helsinki.

Ophthalmic and clinical examinations

All patients underwent complete ophthalmic examinations, including best-corrected visual acuity (BCVA), tonometry, manifest refraction, slit-lamp biomicroscopy, dilated fundus examination, FP, FA, FAF, SD-OCT, and EDI. The data collected included the presence of hypertension, duration of diabetic mellitus, level of hemoglobin A1c (HbA1c), presence of chronic kidney disease (CKD), and insulin use. The presence of CKD was defined as microalbuminuria or an estimated glomerular filtration rate of less than 90 mL/min/1.73 m^2 [19].

Fundus autofluorescence imaging

FAF was obtained using a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph 2; Heidelberg Engineering, Heidelberg, Germany) in a routine clinical setting. A 30 × 30° area centered at the fovea was scanned using excitation with a 488-nm argon laser and 500-nm filter. The ART [automatic real time] module (Heidelberg Engineering) was used to average 30 to 100 scanned images to ensure sufficient quality.

Choroidal and retinal thickness measurements

All patients underwent SD-OCT examination, including EDI. RT and CT were measured by two independent investigators blinded to the DRPE and PDR group allocations, and the mean value

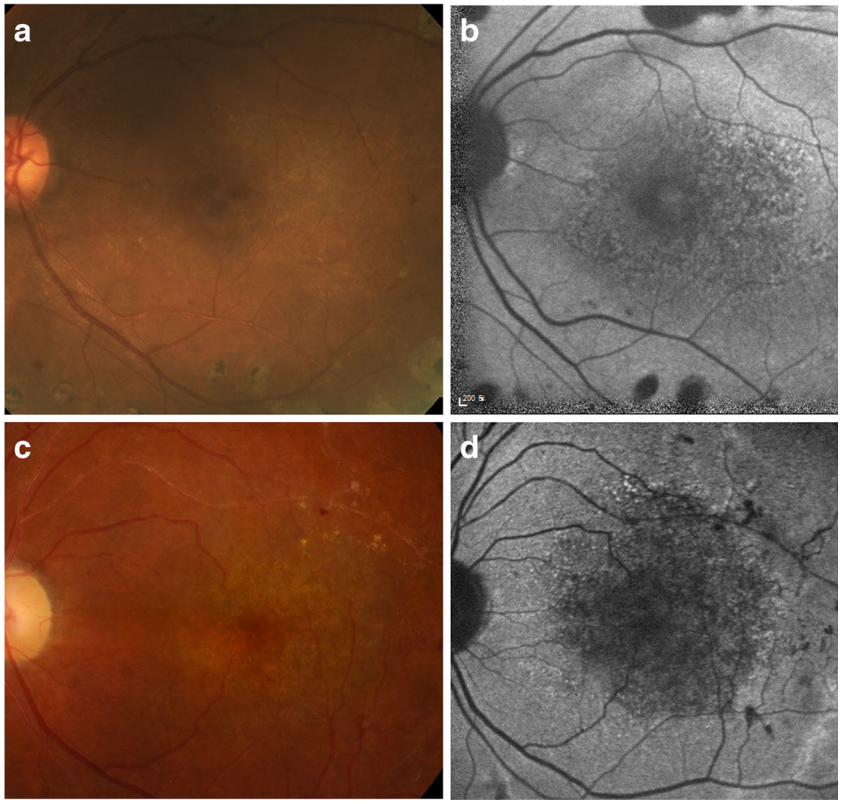

Fig. 1 Two patterns of abnormal autofluorescence (AF) on fundus autofluorescence (FAF) were observed. **a**, **b** Images of the left eye acquired from a 59-year-old man with diabetic retinal pigment epitheliopathy (DRPE). **c**, **d** Images of the left eye of a 60-year-old man with DRPE. **b** FAF shows diffuse granular hypo-AF with variable hyper-AF at the macula. **d** FAF shows diffuse granular hypo-AF surrounded by minimal focal hyper-AF

measured by the investigators was used for the statistical analysis. The intraclass correlation coefficient was 0.937, indicating excellent agreement between investigators. RT and CT were measured from the fovea to parafovea (a distance of 1500 μm from the foveal center) at 500-μm intervals using the caliper tool in the OCT Heidelberg Eye Explorer (HEYEX) software (Heidelberg Engineering). The thickness of the RPE and the inner segments (IS) and outer segments (OS) of the photoreceptors were measured by the vertical distance from the outer edge of the RPE to the outer edge of the external limiting membrane (ELM). The thickness of the outer nuclear layer (ONL) and outer plexiform layer (OPL) was measured from the ELM to the inner edge of the OPL. Inner retinal thickness was measured from the outer edge of the inner nuclear layer (INL) to the internal limiting membrane (ILM), except for the foveal center, because of the lack of inner retinal components.

The perpendicular distance from the outer edge of the hyperreflective RPE to the hyperreflective line of the choroid-scleral junction was measured manually using the caliper CT measurement tool.

Statistical analysis

The results are expressed as the mean ± standard error of the mean. The Mann–Whitney *U* test was used to compare the quantitative data, including duration of diabetes, HbA1c level, visual acuity (VA), mean spherical equivalent, intraocular pressure, CT, and RT. Categorical values including insulin use and the presence of hypertension or CKD were compared using Fisher's exact test. All analyses were performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA), and a *P* value less than 0.05 was considered statistically significant.

Results

Baseline characteristics

Among the 34 eyes of the 20 patients included in this study, 17 eyes were included in the DRPE group, and 17 age- and sex-matched eyes were included in the PDR group. As stated in the "Patients/Method" section, eyes in this study had been treated with PRP at least 12 months earlier, and the mean age was 59.3 ± 9.4 years in both groups. Mean diabetes duration, mean HbA1c level, mean spherical equivalent, intraocular pressure (IOP), insulin use, and the presence of hypertension or CKD did not differ significantly between the DRPE and PDR groups. However, the mean BCVA was significantly reduced in the DRPE group versus the PDR group ($P = 0.026$; Table 1). The demographics and clinical characteristics of patients in the DRPE group are presented in Table 2.

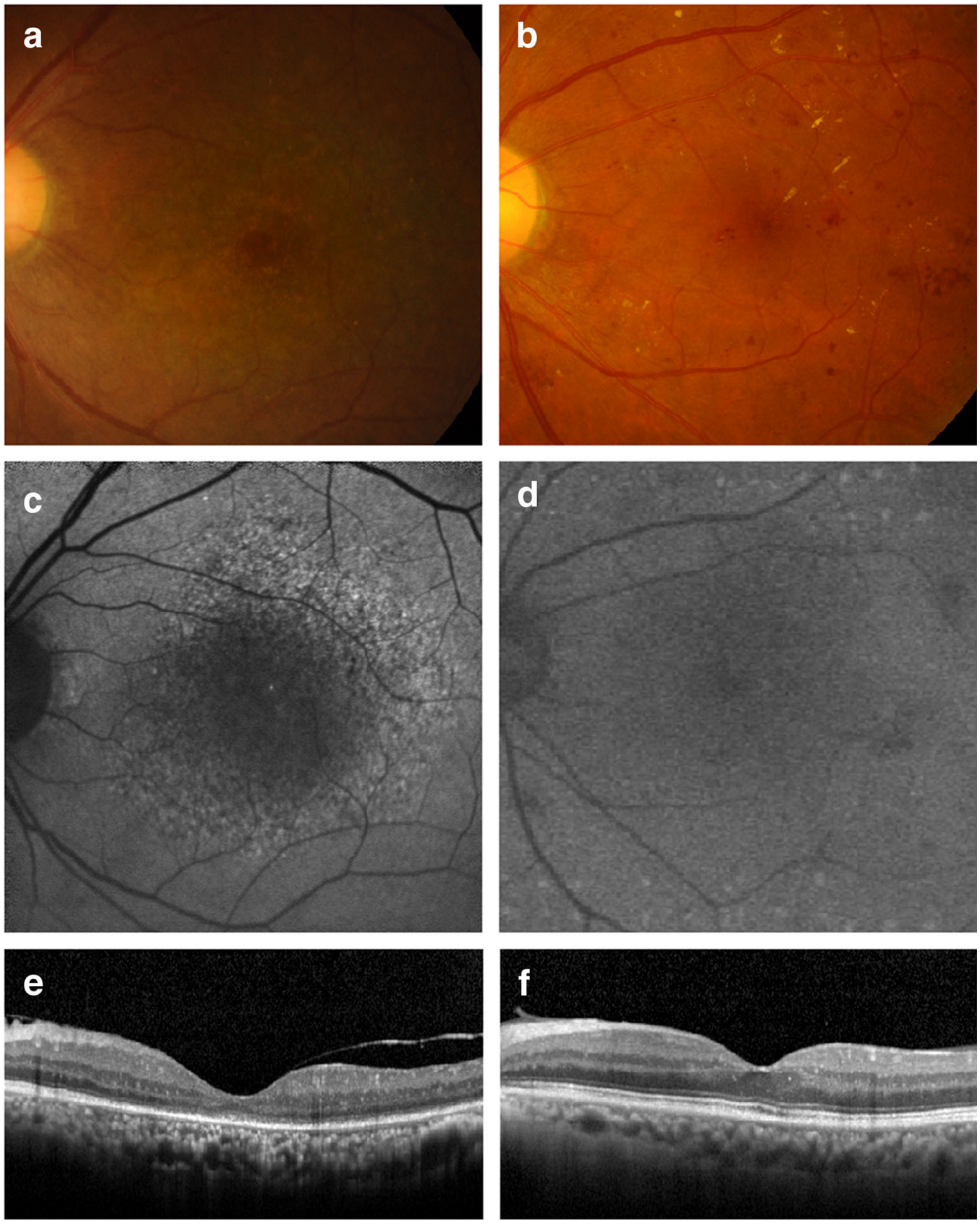

Fig. 2 Representative cases of diabetic retinal pigment epitheliopathy (DRPE) and proliferative diabetic retinopathy (PDR). **a**, **c**, **e** Images of the left eye of a 70-year-old woman with DRPE. **b**, **d**, **f** Images of the left eye obtained from a 60-year-old man with PDR. **a** A fundus photograph shows an alteration in the retinal pigment epithelium (RPE) at the macula. **b** A fundus photograph shows hard exudates with multiple dot hemorrhages, but no abnormal RPE changes. **c** A fundus autofluorescence (FAF) image shows multiple hypo-autofluorescent spots at the macula with some hyper-autofluorescent spots. **d** An FAF image shows no abnormal autofluorescent spot at the macula. **e** Spectral-domain optical coherence tomography (SD-OCT) shows thinning of the RPE and inner segments/outer segments (IS/OS) of the photoreceptors corresponding to the hypo-autofluorescent spots on FAF. The thickness of the outer nuclear layer (ONL) and outer plexiform layer (OPL) are also reduced. **f** The RPE, IS/OS of the photoreceptors, ONL, and OPL are well preserved on SD-OCT

Retinal thickness

The thickness of the RPE + IS/OS was decreased in the DRPE versus PDR eyes at 1500 μm nasal to the fovea (73.24 ± 12.46 vs. 86.38 ± 6.91; $P = 0.001$), 1000 μm nasal to the fovea (71.03 ± 14.43 vs. 91.12 ± 5.41; $P < 0.001$), 500 μm nasal to the fovea (73.21 ± 12.68 vs. 97.18 ± 6.04; $P < 0.001$), the center of the fovea (84.06 ± 15.45 vs. 109.30 ± 11.43; $P < 0.001$), 500 μm temporal to the fovea (68.09 ± 16.30 vs. 93.18 ± 6.96; $P < 0.001$), 1000 μm temporal to the fovea (62.09 ± 11.44 vs. 90.68 ± 8.03; $P < 0.001$), and 1500 μm temporal to the fovea (63.18 ± 12.24 vs. 88.21 ± 7.42; $P < 0.001$; Fig. 3a). The OPL + ONL was thinner in eyes in the DRPE versus PDR group at 1500 μm nasal to the fovea (88.47 ± 12.58 vs. 106.68 ± 16.13; $P < 0.001$), 1000 μm nasal to the fovea (91.06 ± 14.43 vs. 115.68 ± 12.58; $P < 0.001$), 500 μm nasal to the fovea (95.35 ± 19.83 vs. 126.53 ± 14.62; $P < 0.001$), the center of the fovea (117.38 ± 27.61 vs. 141.76 ± 17.39; $P = 0.013$), 500 μm temporal to the fovea (87.88 ± 19.07 vs. 118.34 ± 14.03; $P < 0.001$), 1000 μm temporal to the fovea (84.24 ± 17.86 vs. 110.19 ± 12.53; $P < 0.001$), and 1500 μm temporal to the fovea (81.85 ± 17.27 vs. 103.35 ± 10.04; $P < 0.001$; Fig. 3b). In contrast, the thickness of the inner retina was not significantly different between the DRPE and PDR groups at 1500 μm nasal to the fovea (177.44 ± 43.91 vs. 162.50 ± 30.10; $P = 0.106$), 1000 μm nasal to the fovea (174.35 ± 36.52 vs. 157.59 ± 29.92; $P = 0.231$), 500 μm nasal to the fovea (119.21 ± 28.56 vs. 112.18 ± 24.11; $P = 0.290$), 500 μm

Table 1 Baseline characteristics of patients

Characteristic	Group		*P* value
	DRPE	PDR	
No. of eyes (patients)	17 (10)	17 (10)	
Gender (M/F)	6/4	6/4	
Mean age ± SD (years)	59.3 ± 9.4	59.3 ± 9.4	1.000
Mean diabetes duration (years)	20.3 ± 7.38	19.3 ± 8.4	0.579
Mean HbA1c (%)	7.65 ± 1.59	7.11 ± 0.96	0.762
BCVA (logMAR)	0.369 ± 0.266	0.185 ± 0.119	0.026
Mean spherical equivalent (Diopter)	0.64 ± 0.84	0.29 ± 0.75	0.260
IOP (mmHg)	13.8 ± 2.8	12.8 ± 2.3	0.394
No. of patients with HT (%)	7 (70)	5 (50)	0.361
No. of patients who use insulin (%)	3 (30)	2 (20)	0.606
No. of patients with CKD (%)	6 (60)	6 (60)	1.000

BCVA best-corrected visual acuity, *CKD* chronic kidney disease, *DRPE* diabetic retinal pigment epitheliopathy, *HbA1c* hemoglobin A1c, *HT* hypertension, *IOP* intraocular pressure, *logMAR* logarithm of the minimum angle of resolution, *PDR* proliferative diabetic retinopathy, *SD* standard deviation

temporal to the fovea (115.00 ± 30.16 vs. 113.16 ± 25.61; $P = 0.837$), 1000 μm temporal to the fovea (169.53 ± 27.34 vs. 148.97 ± 32.24; $P = 0.101$), or 1500 μm temporal to the fovea (176.15 ± 40.20 vs. 155.18 ± 34.96; $P = 0.140$; Fig. 3c).

Choroidal thickness

CT was significantly increased in eyes in the DRPE group compared with those in the PDR group at 1500 μm nasal to the fovea (277.18 ± 50.97 vs. 182.50 ± 41.26; $P < 0.001$), 1000 μm nasal to the fovea (301.12 ± 44.75 vs. 198.38 ± 39.07; $P < 0.001$), 500 μm nasal to the fovea (315.44 ± 41.85 vs. 213.24 ± 38.15; $P < 0.001$), the subfoveal region (329.00 ± 33.76 vs. 225.62 ± 37.47; $P < 0.001$), 500 μm temporal to the fovea (322.56 ± 38.69 vs. 218.24 ± 38.48; $P < 0.001$), 1000 μm temporal to the fovea (320.56 ± 39.82 vs. 207.00 ± 36.40; $P < 0.001$), and 1500 μm temporal to the fovea (299.85 ± 43.32 vs. 195.06 ± 32.83; $P < 0.001$; Fig. 3d).

Table 2 Demographic and clinical characteristics of patients with DRPE

Case	Age	Sex	Systemic disease	Duration of DM	Level of HgA1c	Study eye	IOP	Mean SE	Snellen VA	SFCT (μm)	SFRT (μm)
1	62	Female	HT, CKD	22	6.4	Left	11	−0.37	20/63	288	149
2	60	Male	HT, CKD	21	6.6	Right	11	1.13	20/40	373	224
3	70	Female	HT	16	6.7	Right	14	1.25	20/50	332	128
						Left	15	1.50	20/50	313	177
4	68	Male	HT, CKD	25	8.0	Right	16	2.63	20/50	331	229
						Left	15	1.88	20/50	331	247
5	57	Female	HT, CKD	31	6.7	Right	9	0.00	20/100	355	172
						Left	11	0.00	20/40	342	248
6	59	Male	HT	20	6.4	Right	17	0.00	20/32	304	203
						Left	19	0.00	20/32	323	241
7	59	Male	HT, CKD, B-virus carrier	25	9.9	Right	10	0.25	20/32	374	222
						Left	12	1.00	20/63	301	225
8	56	Female	none	13	11.0	Right	14	0.00	20/100	288	179
						Left	14	0.00	20/200	295	135
9	66	Male	CKD	25	7.2	Right	17	1.25	20/20	401	207
10	36	Male	none	5	7.6	Right	14	0.00	20/20	292	225
						Left	15	0.00	20/25	356	234

CKD chronic kidney disease, *DM* diabetes mellitus, *DRPE* diabetic retinal pigment epitheliopathy, *HbA1c* hemoglobin A1c, *HT* hypertension, *IOP* intraocular pressure, *logMAR* logarithm of the minimum angle of resolution, *SE* spherical equivalent, *SFCT* subfoveal choroidal thickness, *SFRT* subfoveal retinal thickness, *VA* visual acuity

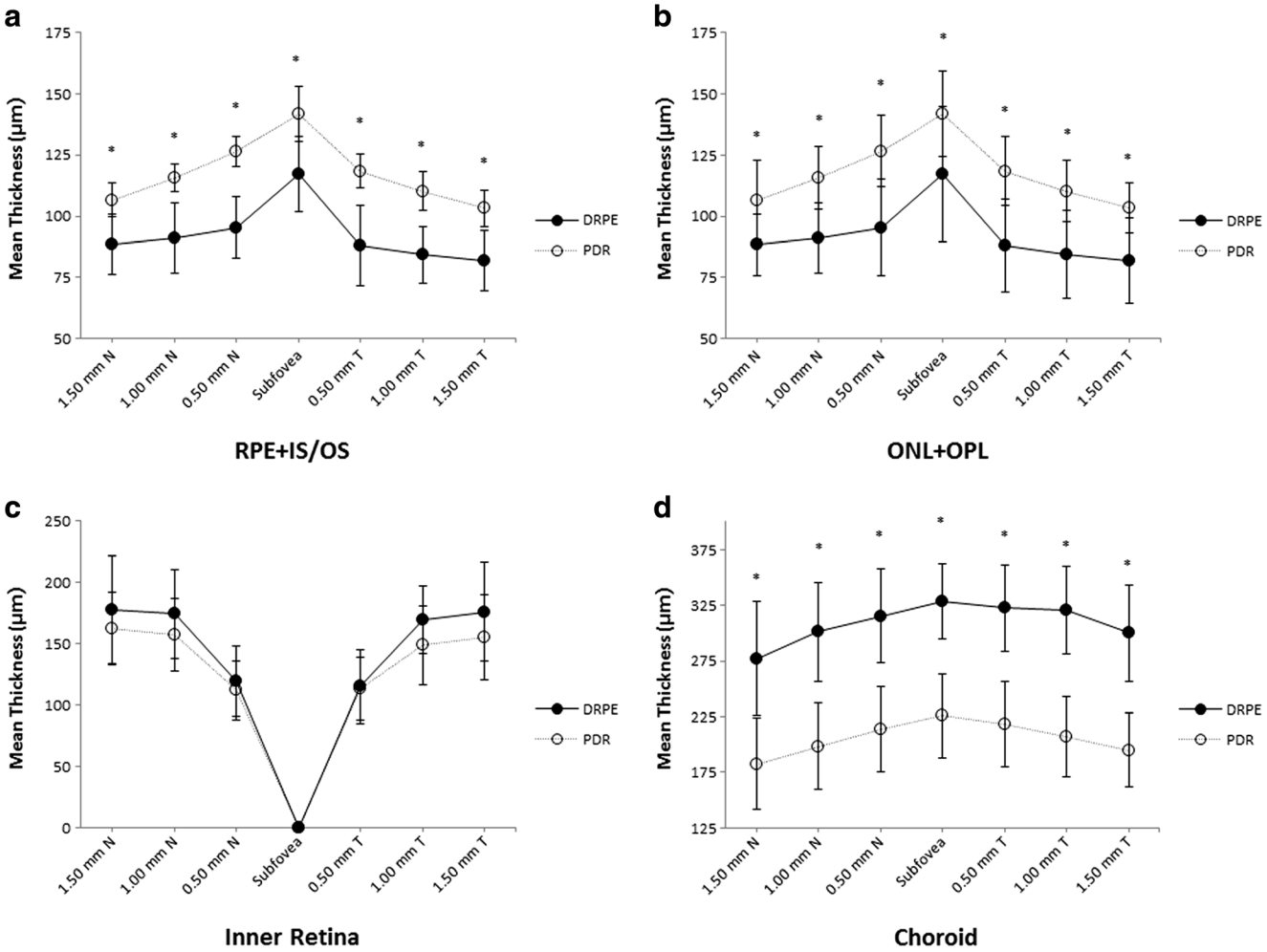

Fig. 3 Graphs show retinal thickness (RT) and choroidal thickness (CT) obtained by spectral-domain optical coherence tomography (SD-OCT) from 1500 µm nasal (N) to the fovea to 1500 µm temporal (T) to the fovea at 500-µm intervals in eyes with diabetic retinal pigment epitheliopathy (DRPE) and proliferative diabetic retinopathy (PDR). **a** Mean thickness of the retinal pigment epithelium (RPE) and the inner/outer segments (IS/OS) of the photoreceptors in eyes with DRPE and PDR. The RPE and IS/OS layer were thinner in eyes with DRPE than those with PDR at all locations. **b** The mean thickness of the outer nuclear layer (ONL) and outer plexiform layer (OPL) in eyes with DRPE and PDR. The ONL and OPL in were thinner in DRPE versus PDR eyes at all locations. **c** Mean thickness in eyes with DRPE and PDR. There was no difference between the two groups. **d** Choroidal thickness in eyes with DRPE and PDR. Choroidal thickness was greater in the DRPE group versus PDR group at all locations. * Indicates a significant difference in mean thickness between the two groups

Representative cases of DRPE

Case 1

A 60-year-old woman with a history of diabetes for 20 years and hypertension for 10 years presented with decreased VA in her right eye caused by vitreous hemorrhage for 2 weeks. On examination, Snellen BCVA was 2/20 in the right eye and 8/20 in the left eye. The right eye was hazy when visualized because of vitreous hemorrhage and the left eye showed multiple dot and blot hemorrhages under dilated funduscopic examination. New vessels in both eyes were noted on fluorescein angiograms, and panretinal photocoagulation was performed on the left eye. In addition, trans pars plana vitrectomy was performed on the right eye for the vitreous hemorrhage. The left eye showed no definite anatomical abnormalities under SD-OCT (Fig. 4a), but decreased BCVA was noted. At 2 years of follow-up, the Snellen BCVA of the left eye had slightly worsened, to 6/20, and FAF was undertaken because of RPE changes under funduscopic examination, and the presence of multiple granular hypo-AF dots with surrounding hyper-AF dots at the macula was noted in FAF (Fig. 2c). An image acquired on SD-OCT showed atrophy in the RPE and IS/OS of the photoreceptors around the fovea and thinning of the ONL + OPL (Fig. 2e). At 4 years of follow-up, the BCVA of the left eye had not changed, but progressive outer retinal atrophy and dilatation of large choroidal vessels were noted on SD-OCT (Fig. 4c). Serial images from the first visit through 4 years of follow-up are displayed in Fig. 4.

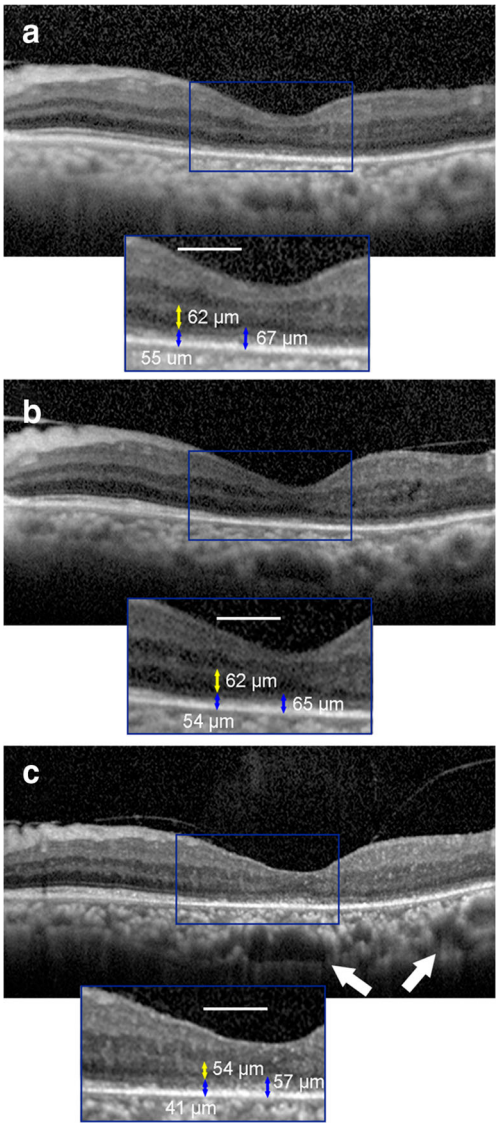

Fig. 4 Series of spectral-domain optical coherence tomography (SD-OCT) images from a 62-year-old woman with diabetic retinal pigment epitheliopathy. **a** An image from the first visit shows that the layer of the retinal pigment epithelium (RPE) and inner segments/outer segments (IS/OS) of the photoreceptors were relatively maintained. **b** An image obtained at 6 months of follow-up. **c** An image obtained at 4 years of follow-up shows thinning of the outer retina with engorgement of a large choroidal vessel. *Blue arrows* show the reduction in the RPE and IS/OS of the photoreceptor layer from baseline to 4 years of follow-up. *Yellow arrows* depict thinning of the outer retinal layer at 500 μm nasal to the fovea from baseline to 4 years of follow-up. *White arrows* indicate the dilatation of large choroidal vessels. *White bars* are reference lines showing 500 μm

Case 7

A 55-year-old man with a medical history of diabetes for 21 years and hypertension for 5 years and who was a hepatitis B virus carrier was referred for a regular check-up after PRP treatment for PDR in both eyes. On examination, Snellen BCVA was 20/20 in the right eye and 14/20 in the left eye. The findings of the anterior segment examination were not remarkable. The dilated funduscopic examination demonstrated dot and blot hemorrhages, but no apparent DME. FAF and SD-OCT images showed no definite abnormal findings (Fig. 5a, b). At 18 months of follow-up, the patient presented with decreased VA and photopsia in both eyes. Snellen BCVA had decreased to 16/20 in the right eye and 12/20 in the left eye. A dilated funduscopic examination revealed mild RPE mottling changes, but no DME. Some hyper-AF spots were observed in the parafoveal area on FAF and decreased intensity of the IS/OS of the photoreceptor layer on SD-OCT (Fig. 5c, d). At 3 years of follow-up, the patient's BCVA had worsened to 12/20 in the right eye and 6/20 in the left eye. Funduscopic examination showed an increased area of RPE changes at the macula. FAF showed diffuse granular hypo-AF spots with speckled hyper-AF spots at the macula in both eyes (Fig. 5e). There was no DME, but the RPE layer and IS/OS of the photoreceptors were atrophied on SD-OCT (Fig. 5f). At 4 years of follow-up, BCVA remained 12/20 in the right eye and 6/20 in the left eye. FA revealed no new vessels in either eye. The AF abnormalities in the macula on FAF were unchanged from the previous visit (Fig. 5g). However, the thickness of the inner retina, including the RPE, IS/OS of the photoreceptors, ONL, and OPL, was reduced from previous SD-OCT images.

Discussion

In this comparative case series, eyes with DRPE demonstrated worse VA and thinner RPE + IS/OS of the photoreceptors and OPL + ONL than eyes with PDR. In contrast, the thickness of the inner retina did not differ between the DRPE and PDR groups. The DRPE group also exhibited greater CT than the PDR group.

In an earlier animal study, anatomical changes were observed in RPE cells of diabetic rats, which showed deepened hollows in the basal infoldings [9]. A recent study using SD-OCT noted a thinned RPE and IS/OS of the photoreceptors in diabetic patients [20], and another study reported changes in the RPE proteome in preretinopathic diabetic donor eyes [21]. RPE cells of diabetic rats have shown a substantial loss of occludin, a major component of tight junctions [8], resulting in the breakdown of the outer BRB and leading to loss of RPE cell barrier function. Using FA, Weinberger et al. [22] examined 1850 non-proliferative DR patients with extensive leakage, and found that the leakage in 14 patients did not originate from retinal vessels. The authors postulated that leakage may have occurred through the RPE cells, which serve as a barrier between the choriocapillaris and avascular outer retina. However, FA could not differentiate outer BRB-specific leakage, as the leakage of fluorescein through the retinal endothelial cells caused a buildup of fluid in the inner BRB, which may have obscured leakage from the RPE cells. FAF has been

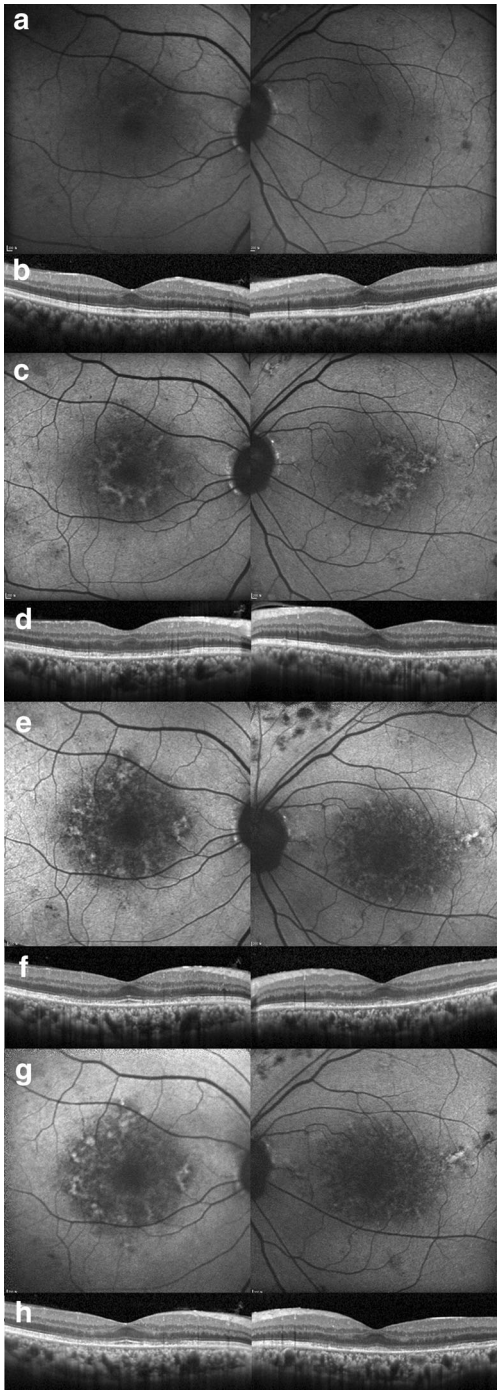

Fig. 5 A representative case (Case 7): a 55-year-old man with diabetic retinal pigment epitheliopathy (DRPE). **a** Fundus autofluorescence (FAF) at the first visit showed no definite abnormality in either eye. **b** At the first visit, the horizontal scan from spectral-domain optical coherence tomography (SD-OCT) demonstrated no apparent abnormality. **c** At 18 months of follow-up, FAF showed increased parafoveal autofluorescence (AF). **d** At 18 months of follow-up, SD-OCT showed irregularities and decreased intensity in the inner segment/outer segment (IS/OS) layers of the photoreceptors. **e**, **g** At 3 and 4 years of follow-up, diffuse granular hypo-AF with speckled hyper-AF was observed in the macula on FAF. **f**, **h** At 3 and 4 years of follow-up, SD-OCT showed progressive thinning of the outer retina, including the retinal pigment epithelium and IS/OS of the photoreceptors, outer nuclear layer, and outer plexiform layer

used as a non-invasive diagnostic tool for the detection of early RPE dysfunction in various diseases, including AMD, CSC, and drug-related retinal toxicity. FAF is generated by the excitation of lipofuscin, a byproduct of the phagocytosis of the OS of the photoreceptors, using an argon laser light (488 nm) [11].

Our study revealed that eyes in the DRPE group, which had multiple abnormal AF in the macula, showed a thinner RPE and IS/OS of the photoreceptors and lower VA than eyes in the PDR group. Studies have shown that multiple hypo-AF spots on FAF can result from reduced lipofuscin caused by the loss of RPE, RPE dysfunction [12], or the atrophied OS of photoreceptors [11, 23]. SD-OCT has also shown that hypo-AF spots correspond with the area of RPE atrophy or disruption of IS/OS in eyes with DRPE (Fig. 2e). Atrophy or disruption of the RPE and IS/OS complex can reduce VA, as our study demonstrated. In addition, there was variable hyper-AF in the macula and around the margin of the diffuse granular hypo-AF area. Hyper-AF might be induced by increased phagocytosis of photoreceptor OS in abnormal RPE cells, and could be replaced by hypo-AF with progressive RPE damage [11, 12].

Multiple mechanisms can induce anatomical and functional abnormalities in RPE cells in diabetes. First, DC can cause RPE cell damage. The presence of DC is positively associated with the severity of DR [7], and thus eyes with PDR, which is a severe form of DR, can have DC concurrently. A histopathological study revealed that DC was characterized by obstruction of the choriocapillaris and small choroidal vessels with thickening of the basement membrane [24]. Narrowing or obstruction of the choriocapillaris was found to lead to early hypo-fluorescent spots and late choroidal non-perfusion regions on indocyanine green angiography (ICGA) [7, 25]. Reduced choroidal blood flow was also noted in early DR in a mouse model of diabetes [26]. It is possible that reduced choroidal circulation in DC would result in an insufficient supply of nutrients to the RPE and photoreceptors, which consume most of the oxygen [1]. Another possible mechanism influencing RPE function and morphology is increased vascular endothelial growth factor (VEGF) in DR. Eyes with PDR are characterized by neovascularization of the disc and elsewhere [4], and elevated VEGF levels in the vitreous and plasma [27]. Increased VEGF-A levels in mice were found to contribute to anatomical changes in RPE cells and retinal thinning [28]. VEGF also led to a reduction in fluid resorption and an increase in RPE cell leakage [29]. A third mechanism associated with RPE cell damage is overload and dysregulation of iron. Chronic venous congestion can occur in DRPE, and induces extravasation of erythrocytes, which contain a high level of iron [30]. Interstitial macrophages that degrade erythrocytes and iron can be released into the extracellular matrix space around the choriocapillaris. Diabetic patients also show increased serum levels of ferritin, which represents iron stores in the body, and ceruloplasmin, which acts as an antioxidant

by converting ferrous iron (Fe^{+2}) to less toxic ferric iron (Fe^{+3}) [31]. An increased iron level can thus be attributed to the generation of various reactive oxygen species (ROS) and nitrogen species, and oxidative stress caused by these species can damage the RPE and OS [32].

CT in diabetes is influenced by various factors, including age, spherical equivalent, the stage of DR, the presence of DME, and treatment of PRP [14–17]. Though there were no differences in these factors between the DRPE and PDR groups in our study, CT was greater in the DRPE group than the PDR group. There are three possible explanations for this. First, an increase in CT due mainly to dilatation of large choroidal vessels (Haller's layer) may be a cause of DRPE. In this study, multiple engorged large choroidal vessels were observed in eyes with DRPE compared with eyes with PDR (Fig. 4c), which may be associated with obliteration of the choriocapillaris and medium-sized choroidal vessels (Sattler's layer) [33]. Atrophy in the inner choroid may cause damage to the RPE and result in DRPE. Dilatation of the choroidal vessels has similarly been suggested in the pathogenesis of pachychoroid pigment epitheliopathy (PPE), which exhibits RPE abnormalities and choroidal thickening [34]. Second, choroidal hyperpermeability and congestion in DRPE can induce choroidal thickening. DR is associated with inflammation, elevated systemic cytokines such as TNF-α and IL-β, and elevated numbers of circulating leukocytes [35]. Intercellular adhesion molecule-1 (ICAM-1) and P-selectin, which play critical roles in the adhesion of leukocytes to the vascular endothelium, are up-regulated in the choroidal vasculature in diabetes [36]. Leukocytes adhere to choroidal endothelial cells, and oxidative burst activity in polymorphonuclear leukocytes kills these cells [37], resulting in the leakage of proteins into the extracellular matrix of the choroid, and increasing CT and congestion from passive fluid flow [1]. In addition, an in vivo study demonstrated a significant increase in transendothelial permeability in choroidal endothelial cells when a high glucose condition was induced [38]. Third, an increased VEGF level in DRPE can increase CT. It is well known that eyes with PDR contain a high level of VEGF in the vitreous, and a high glucose status in diabetes promotes the expression of VEGF in RPE cells [39, 40]. Elevated VEGF alters the outer barrier function of the RPE [28, 29], and an influx of VEGF into the choroid increases capillary permeability. One study reported a positive correlation between macular CT and intraocular VEGF levels, which supports this hypothesis [41].

In the present study, the ONL and OPL were thinner in the DRPE group than the PDR group. This reduction in thickness could be the result of both compromised choroidal blood flow and RPE dysfunction associated with DRPE. On the other hand, there was no difference in inner retinal thickness between the two groups, as the inner retina is supplied by retinal circulation.

This study has certain limitations. First, it is a comparative case series, with a small sample size. We included age- and sex-matched controls (17 eyes) to balance the baseline characteristics and inherent selection bias that may have occurred. In addition, we could not evaluate the degree and size of abnormal AF on FAF, as we defined abnormal AF qualitatively rather than quantitatively. Because FAF signals can be reduced by macular pigments such as lutein or zeaxanthin, which are concentrated at the central retina [11, 42], FAF cannot detect subtle changes in RPE cells near the foveal center or in early diabetic eyes. Moreover, the hyperpermeability of the choroid, which may be a cause of choroidal thickening, was not evaluated by ICGA. Additionally, the VEGF level, which was proposed as a possible factor for RPE abnormality and increased CT, was not compared between the groups. Further research should be performed to determine risk factors for the progression of DRPE.

In conclusion, we report an unfamiliar disease entity, diabetic retinal pigment epitheliopathy (DRPE), in which eyes with DRPE demonstrated multiple hypo-AF and/or variable hyper-AF spots in the macula on FAF. These eyes tended to show decreased VA, thinning of the outer retina (the RPE, IS/OS of the photoreceptors, ONL, and OPL), and choroidal thickening. The study also showed that DC, the clinical significance of which had not been clarified, could induce RPE damage and choroidal thickening. Non-invasive FAF was found to be helpful in diagnosing DRPE in PDR by providing clues as to RPE dysfunction, in contrast to the invasive FA procedure, which can mask RPE abnormalities from retinal vascular leakage.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Informed consent For this type of study, formal consent is not required.

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