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AGE-RELATED RETINAL PIGMENT EPITHELIUM DISEASE

Clinical and Differential Features

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Purpose: We described the clinical characteristics of age-related retinal pigment epithelium disease (ARPED). This looks like an age-related, retinal disease showing a primary RPE involvement, no typical age-related macular degeneration features, and no pachychoroid-related characteristics.

Methods: The study was designed as observational, both cross-sectional and retrospective investigation. We collected data from patients affected by ARPED, defined by precise diagnostic criteria. We performed both qualitative and quantitative multimodal retinal imaging investigations. The main outcome measure is the characterization of ARPED, defined by precise diagnostic criteria, about age-related macular degeneration. Secondary outcome is the identification of differential diagnostic features about other retinal diseases.

Results: We included 31 ARPED eyes (62 patients). Intergraders agreement for detecting ARPED was 0.98 ($P < 0.05$). Age-related retinal pigment epithelium disease is characterized by the absence of age-related macular degeneration–related findings, such as drusen and pseudodrusen. Moreover, it is characterized by the absence of pachychoroid-related features, as also confirmed by fluorescein angiography and indocyanine green angiography.

Conclusion: Although further studies are warranted to better define ARPED features and if it may be considered a distinct macular disease, the characteristics of this clinical phenotype introduce new intriguing pathophysiologic features and should be carefully considered both in clinical practice and research contexts.

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Retinal pigment epithelium (RPE) represents the main support to retinal photoreceptors. This layer may be involved in many pathogenetic cascades leading to retinal diseases. Among these, age-related macular degeneration (AMD) is the most frequent subtype. Indeed, AMD is a leading cause of vision loss in developed countries.[1] In AMD, RPE cells may be damaged by apoptotic, necrotic, and pyroptotic mechanisms.[2–4] In addition, mitochondrial dysfunctions and autophagic processes have been also described.[5,6]

After the progression of the primary disease, RPE cells may undergo atrophy or upregulation of vascular endothelial growth factor (VEGF) production, leading to the onset of possible complications.[7,8] Moving beyond RPE alterations, AMD is classically defined by precise clinical and imaging characteristics, including the presence of different types of debris, such as drusen, pseudodrusen, and basal laminar deposits.[1]

We identified a subgroup of patients characterized by age-related RPE changes, showing no peculiar signs of AMD, such as drusen and pseudodrusen. Moreover, this subgroup of patients showed no morphologic features suggesting other possible known causes, such as pachychoroid-related diseases. To make easier the readability of the paper, here we named this condition as age-related retinal pigment epithelium degeneration (ARPED).

The purpose of this exploratory study is to describe the clinical and multimodal retinal imaging features of ARPED, its clinical impact and highlighting the morphologic differences about other known macular diseases.

Materials and Methods

We performed an observational, both cross-sectional and retrospective investigation, focused on the collection of ARPED cases. All the patients were recruited at the Ophthalmology Unit of IRCCS San Raffaele Scientific Institute (Milan) and signed an informed consent before the inclusion in the study. The entire study was conducted in agreement with good clinical practice and Helsinki declaration, and it was approved by the local ethical committee (protocol ID: MIRD2020).

Diagnostic Criteria to Identify Age-Related Retinal Pigment Epithelium Degeneration

Age-related retinal pigment epithelium degeneration was defined as the presence of posterior pole outer retinal alterations defined by the following criteria: age-related (onset age>50 years), no AMD-related distinctive features (drusen, pseudodrusen, basal laminar deposits), no pachychoroid, no pachyvessels, no history of drugs, or other causes with proven retinal toxicity (e.g., environment exposure or infections). The presence of AMD-related distinctive features was assessed on pharmacologically dilated fundus examination and multimodal retinal imaging data.

We considered only eyes with a refractive error included between −3.0 D and +1.5 D, to avoid possible issues related with too abnormal axial lengths. In pseudophakic cases, we used clinical records to verify that the refractive status of the patients before cataract surgery was included in the above-mentioned refractive range.

Exclusion criteria were the positive history of central serous chorioretinopathy or other retinal disorders, the positive history of posterior uveitis, infections or inflammatory retinopathies,[9] glaucoma or other ocular diseases, uncontrolled systemic conditions potentially affecting the results of the study, previous systemic infections potentially showing ocular involvement (e.g., tuberculosis), and high media opacity. We have also excluded cases showing macular neovascularization, since it could alter the presence of defining AMD features.

We have also considered the consensus diagnostic criteria established by Cheung et al (2021)[10] to exclude polypoidal choroidal vasculopathy. Moreover, we performed next-generation sequencing examination to exclude the presence of pathogenic variants configuring the diagnosis of inherited retinal diseases.

Since a consensus definition of pachychoroid and pachyvessels has not yet been reached, we have formulated our definition based on existing literature to standardize the assessment by our graders. First of all, for the entire cohort of included eyes, we considered fluorescein and indocyanine green angiographies to assess the presence of central serous chorioretinopathy or other pachychoroid-related distinctive features. Moreover, we adopted also optical coherence tomography (OCT)-based criteria to exclude pachychoroid.[11] We considered pachychoroid as a diffusely thick choroid (mean choroidal thickness [CT] >350 μm) with abnormally dilated Haller layer and attenuated Sattler layer.[11] About pachyvessels, we considered focal dilated Haller layer with obliteration of the overlying Sattler layer and vascular diameter of a single pachyvessel >250 μm.[11] The objective assessment of the obliteration of the overlying Sattler layer is challenging because of the lack of standardized methodology. We have arbitrarily defined Sattler layer obliteration as the reduction of at least 50% of the Sattler layer thickness above the pachyvessel compared with the normal appearing choroid on the left and right sides of the same pachyvessel on horizontal OCT scan.

It was mandatory to respect the selected diagnostic criteria for both eyes, considering the study visit and all previously available follow-ups. The evaluation of both eyes has been done to verify the bilateral presence of inclusion/exclusion diagnostic criteria and to assess the symmetric/asymmetric course of the disease.

Cross-Sectional Data Collection

All the eyes underwent complete ophthalmologic assessment of anterior and posterior segments, best-corrected visual acuity, and intraocular pressure measurement.

Multimodal retinal imaging included OCT (high-resolution radial, raster and dense scans, ART >

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25), blue-light fundus autofluorescence, infrared images, near infrared fundus autofluorescence, confocal multicolor, and OCT angiography (high-resolution 15 × 15° scans) (HRA2+OCT Spectralis Heidelberg, Heidelberg Eng, Heidelberg, Germany). Manufacturer quality tools were used to include only high-quality data.

Two expert blinded graders (E.A., M.B.P.) verified the diagnostic criteria for both eyes. Intergrader correlation coefficient has been calculated to verify the interobserver agreement. In case of disagreement, a third grader (F.B.) has been involved.

The qualitative analysis, performed in the entire cohort of eyes, included the assessment of OCT, blue-light fundus autofluorescence and near infrared fundus autofluorescence characteristics, and OCT angiography-based vascular plexa assessment. The following OCT features have been considered: drusen, pseudodrusen, basal laminar deposits, pachychoroid, pachyvessels, RPE hypertrophy, outer retinal atrophy (>250 μm), and fibrosis. We have also calculated the inner retinal layer thickness and outer nuclear layer thickness, based on automatic segmentations provided by HEYEX manufacturer software.

Choroidal thickness was calculated from the mean of five measures performed on a horizontal OCT scan: subfoveal, 750 μm (nasal and temporal) and 1500 μm (nasal and temporal).

Moreover, we calculated vessel density (VD) starting from OCT angiography-based reconstruction of the superficial capillary plexus, deep capillary plexus, and choriocapillaris, by using mean binarization threshold and standard VD calculation procedure.[12]

Data Analysis

For the statistical analysis (SPSS software package, SPSS, Chicago, IL), we verified the normality distribution of the variables through quantile–quantile and histogram plots. Continuous variables were expressed as mean (SD), whereas categorical variables were expressed as frequencies and proportions. Age and gender were considered as fixed factors. Regarding the statistical analysis of the collected quantitative metrics, we included only one randomly selected eye. Statistical significance was set to $P < 0.05$.

Results

We included 31 patients (62 eyes) affected by ARPED. All the involved patients were Whites. The clinical picture revealed hypopigmentation and/or hyperpigmentation abnormalities in the absence of drusen/pseudodrusen at the posterior pole. Dilated fundus examination revealed to clinically relevant peripheral alterations. Fluorescein angiographies and indocyanine green angiographies showed no retinal or choroidal alterations.

Optical coherence tomography scans showed diffuse RPE alterations, together with overlying reflectivity attenuation of the ellipsoid zone and the outer retinal bands. We found a normal appearing choroid with a mean CT of 166 μm (range 131–198 μm), and no evidence of pachychoroid.

Optical coherence tomography angiography showed attenuated deep capillary plexus vessels and high flow voids interesting the choriocapillaris.

Moreover, next-generation sequencing was negative in 100% of cases. Intergrader correlation coefficient agreement regarding the identification of ARPED diagnostic criteria was 0.98 (0.96–0.99) ($P < 0.05$). The involvement of the third grader has never been required. The adopted diagnostic criteria to differentiate ARPED from AMD are listed in Table 1. All the diagnostic criteria have been respected for both eyes of the entire ARPED cohort.

The demographic and clinical characteristics are shown in Table 2. An example case is shown in Figure 1.

The evaluation of the contralateral eye was fundamental to confirm the diagnosis of ARPED. Figure 2 shows two cases where one eye looks like ARPED, but the contralateral eye allowed to exclude the diagnosis of ARPED, because of showing peculiar AMD-related features (Figure 2).

The quantitative imaging data are extensively reported in Table 3. Interestingly, all the ARPED cases resulted characterized by no signs of outer retinal atrophy or fibrosis. In Table 4, we resumed the main ARPED differential diagnosis criteria, about other similar diseases.

Discussion

In the present study, we described ARPED as a clinical phenotype characterized by the absence of classic AMD features, the absence of pachychoroid/pachyvessels, and no history of other ocular or systemic disorders causing the retinal involvement.

The presence of pigmentary alterations allows to hypothesize that the primary alteration resides in a dysfunction of the RPE cells. RPE is fundamental to guarantee the integrity of retinal photoreceptors and choriocapillaris.[16,21] The spectrum of RPE functions includes I) integrity and regulation of outer blood–retinal barrier; II) regulation and protection from oxidative stress; III) transport and distribution of nutrients; IV) phagocytosis of outer photoreceptors segments

Table 1. Diagnostic Criteria to Perform the Differential Diagnosis Between ARPED and AMD

Diagnostic Criteria of ARPED vs. AMD	ARPED	AMD
Age of onset >50	Present	Present
AMD-related distinctive features	Absent	Present
Pachychoroid	Absent	Not mandatory
Pachyvessels	Absent	Not mandatory
History of drugs with proven retinal toxicity	Absent	Not mandatory
History of posterior uveitis or inflammatory retinopathies	Absent	Not mandatory
RPE and outer retinal alterations	Present	Present
Bilaterality	Present	Present
Neovascular complication	Not mandatory	Not mandatory
Atrophy/fibrosis	Not mandatory	Not mandatory

and preservation of the visual cycle; V) production of growth factors and metabolic mediators; and VI) production of cytokines and regulation of inflammatory mechanisms.[7] The progressive dysfunction of these mechanisms is described as the causative factor for the onset and progression of AMD.[7] However, AMD is characterized by the accumulation of peculiar pathologic debris in the early stages of the disease.[22–24]

Based on the present findings, ARPED pathogenesis seems to be mainly characterized by a selective RPE involvement, representing the most evident alteration, not followed by the accumulation of pathologic debris. As a secondary occurrence, the RPE damage may lead to the loss of trophic support to the photoreceptors, thus explaining the attenuation of the outer retinal bands overlying the site of RPE defects.

This pathogenesis also differs from the clinical entity known as age-related choroidal atrophy, recognizing a primary choroidal damage, and being also possibly characterized by pathologic debris.[25]

Although our imaging data cannot provide enough scientific evidence to establish the pathogenesis of ARPED, an intriguing hypothesis came from the concept of cellular senescence. Cell senescence is characterized by strong changes in cell morphology, structural integrity, and metabolic functions. The wide spectrum of alterations has been excellently described by Habibi-Kavashkohie et al,[13] which stressed the importance of these changes in the pathogenesis of macular diseases. One of the first phenomena occurring in senescent cells is the accumulation of cytoplasmic DNA,[26] and this has been already described also in RPE cells.[27,28] For this reason, we might interpret ARPED as a retinal disease primarily driven by the progressive loss of function of RPE cells.

Table 2. Demographic and Clinical Characteristics of ARPED

Demographic and Clinical Characteristics	
No. of patients (eyes)	31 (62)
Age	69 (59–75)
Gender (M/F)	12/19 (40%-60%)
Refraction (diopters)*	+0.75 D (−2.50 to +1.50 D)
LogMAR BCVA (range)	0.1 (0.2–0.0)

Data are reported as mean (range) and proportions (percentages).

*For pseudophakic cases, we used clinical records to take the refractive status before cataract surgery.

BCVA, best-corrected visual acuity.

We are aware that our study is potentially affected by several limitations. First, this study was not designed to describe a new disease. Indeed, this hides many pitfalls and difficulties, requiring further validation of the present results on larger cohorts of patients. For this reason, we do not have the presumption to have provided all the necessary information with this study. Our main purpose was to describe a clinically different phenotype of age-related maculopathy, whether we can consider it AMD. We want to highlight that this phenotype is undoubtedly characterized by the absence of AMD classic features and a less severe clinical course. But again, the retrospective nature of the study and the limited information require further prospective investigations with standardized follow-up and higher number of eyes to support our findings as well to define ARPED as a new macular disease or not. Moreover, many other diseases should be included in the ARPED differential diagnosis. We have collected the diseases that might be most likely to be included in the ARPED differential diagnosis in Table 4.[10,11,14,15,17–19,25,29,30] Although each disease has specific diagnostic criteria, all these retinal diseases should be carefully addressed by future prospective studies, to definitely establish differential features from ARPED. About age-related choroidal atrophy, a clinical finding described by Prof. Spaide[25] in 2009,[25] we would highlight the main features adopted

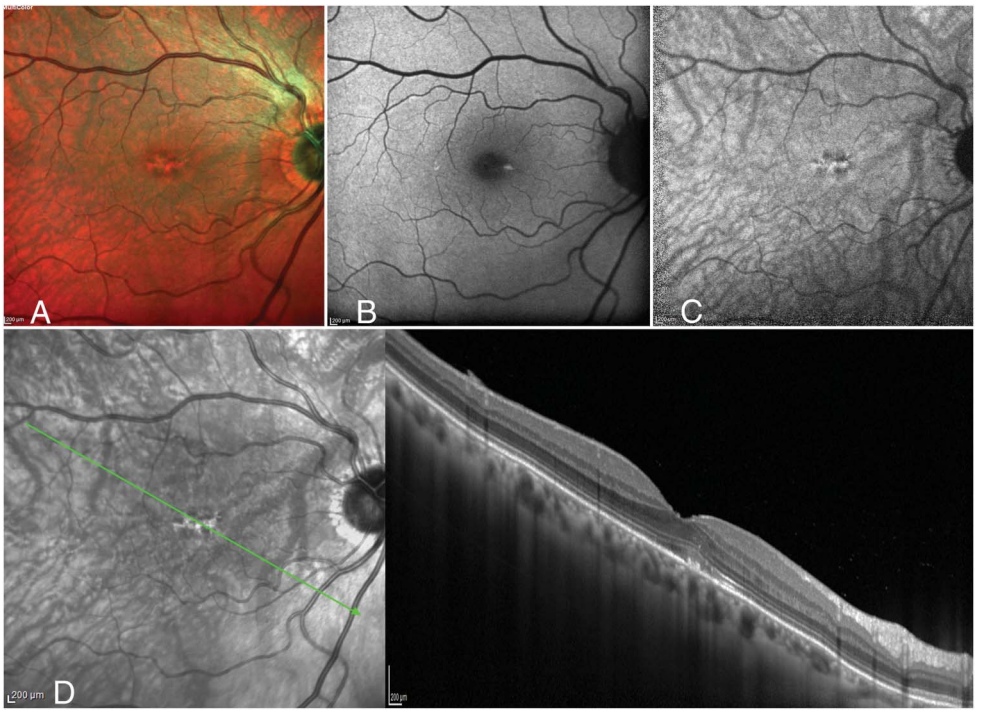

Fig. 1. Example case of ARPED. ARPED is characterized by pigmentary alterations, as revealed by multicolor (**A**), BAF (**B**), and NIR-AF (**C**) images. Structural OCT (**D**) shows the presence of RPE alterations, together with overlying reflectivity attenuation of the outer retinal bands, and a normal appearing choroid. All the imaging modalities confirm the absence of AMD-related alterations in both eyes (contralateral eye not shown in the figure). BAF, blue-light fundus autofluorescence; NIR-AF, near infrared fundus autofluorescence.

as differential diagnostic criteria. Indeed, although mainly representing a disease associated with a thin choroid, age-related choroidal atrophy has been described as associated with tessellated fundus, drusen, and pseudodrusen, which represent exclusion criteria for ARPED. Moreover, CT has been mandatorily described as lower than 125 μm in age-related choroidal atrophy. Indeed, although mainly representing a disease associated with a thin choroid, age-related choroidal atrophy has been described as associated with tessellated fundus, drusen, and pseudodrusen, which represent exclusion criteria for ARPED. ARPED resulted characterized by a thin choroid, although CT resulted remarkably higher than in age-related choroidal atrophy. On all these bases, we defined ARPED as a distinct clinical entity from age-related choroidal atrophy. About the differential diagnosis with reticular pseudodrusen, we adopted the official criteria provided by the Classification of Atrophy Meetings expert group, defining it as "reflective material accumulating above the RPE in the subretinal space."[20] The OCT characteristics are highlighted by the AMD example provided in Figure 2. ARPED-related OCT alterations look like RPE hypertrophy, resulting completely incorporated in the thickness of RPE band on OCT. However, we have to acknowledge that histology confirmation is needed to define the composition of ARPED-related alterations about drusen and reticular pseudodrusen.

We are also aware about the role of external substances as inductors of retinal toxicity and epitheliopathy. Although we used the history of drugs or environmental compounds with proven retinal toxicity as exclusion criterion, we cannot exclude at all the

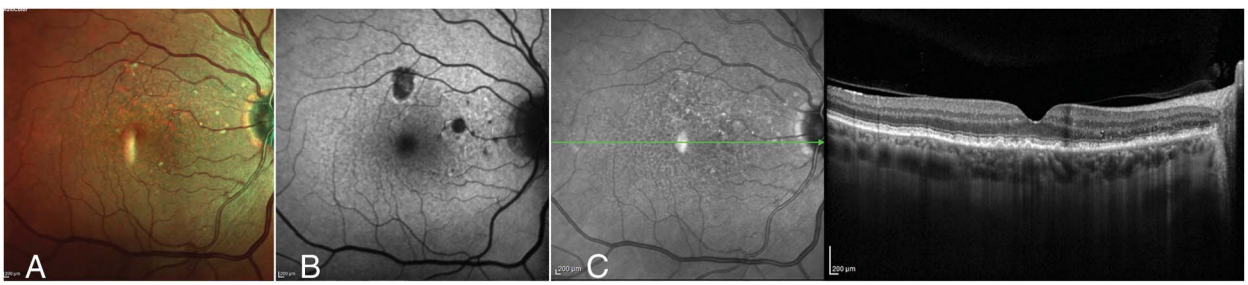

Fig. 2. Example case of classic AMD. The first case shows mild macular alterations both on multicolor (**A**) and BAF (**B**) images. Some atrophic spots are visible in the extramacular region. Structural OCT (**C**) shows the presence of diffuse small drusen and pseudodrusen.

Table 3. Clinical Characteristics of ARPED Eyes

Quantitative analysis	
Total number of eyes	62
No. of included eyes	31
ONL thickness (μm)	95 (85–110)
Inner retinal thickness (μm)	157 (146–169)
Choroidal thickness (μm)	166 (131–198)
SCP VD	0.36 (0.32–0.39)
DCP VD	0.33 (0.29–0.35)
CC VD	0.44 (0.42–0.49)

Data are reported as mean (range) and proportions (percentages).

CC, choriocapillaris; DCP, deep capillary plexus; ONL, outer nuclear layer; RPE, retinal pigment epithelium; SCP, superficial capillary plexus; VD, vessel density.

possible interference of external factors. Although our next-generation sequencing investigation excluded the presence of pathogenic variants, it investigated a limited number of genes. Hence, we cannot exclude at all a still unknown genetic origin of ARPED. We advanced several pathogenic hypotheses supported by the literature. However, further histologic studies are warranted to draw definite conclusion regarding ARPED microstructural characteristics and pathogenesis. Because of the retrospective nature of the study, we could not include axial length measurement. We based our evaluation on refractive status only collected from clinical records (in case of pseudophakic eyes, we considered the refractive error before cataract surgery). Last, we are aware that all noninvasive imaging modalities are potentially prone to artifacts interfering with the proper interpretation of the results.[31]

In conclusion, we described the clinical characteristics of ARPED as a macular condition characterized by a main involvement of RPE, no cases of geographic atrophy or fibrosis, and moderately severe clinical

Table 4. Main ARPED Differential Diagnosis

ARM Differential Diagnosis		
Retinal Disease	Main Distinctive Features	References
Age-related choroidal atrophy	Drusen Pseudodrusen Fundus tessellation	13
Angioid streaks	Not age-related Typical optic nerve fundus findings Bruch membrane weakening and rupture on OCT PEPSI diagnostic criteria	14
Cone–rod inherited retinal dystrophies	Not age-related Genetically determined Often symmetric clinical features	15
Central serous chorioretinopathy	Not age-related Pachychoroid/pachyvessels Possible unilaterality	12,16
Choroidal rupture	Not age-related Usually unilateral Often positive history of ocular trauma No evident alterations on the rest of the retina	17
Idiopathic choroidal neovascularization	Not age-related Often age of onset $<$ 50 years Often unilateral No RPE alterations at the posterior pole Sometimes associated to choroidal abnormalities and inflammation	18
Inflammatory choroidal neovascularization	Not age-related Usually associated with posterior uveitis Possible unilaterality	19
Late-onset Stargardt disease	Possible earlier age of onset ($>$45 years) Genetically determined Often symmetric clinical features Greater tendency to outer retinal atrophy than macular neovascularization Peculiar findings (e.g., flecks)	20
Pachychoroid pigment epitheliopathy	Not age-related Pachychoroid/pachyvessels Possible unilaterality	16

impact. The absence of AMD-related distinctive features supports the hypothesis of ARPED as a distinct phenotype, which might find in RPE dysfunction the primary alteration. However, based on the present findings, we could not assert that ARPED represents an effectively different disease from AMD. Further studies are warranted to better define ARPED characteristics and if it may be considered a distinct macular disease. However, ARPED can be recognized by the criteria adopted in this study and introduced new intriguing pathophysiologic features regarding the pathologic ageing of RPE and outer retina. Hence, regardless of whether ARPED is a separate disease, the characteristics of this clinical phenotype should be carefully considered both in clinical practice and research contexts.

Key words: age, maculopathy, ARPED, AMD, RPE.

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