Multi-Mode Imaging Characteristics And Prognosis of Large Avascular Retinal Pigment Epithelium Detachment (Aped) In Macular Area

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Research Article

Keywords: Avascular, Retinal pigment epithelium detachment (PED), Serous, Drusenoid

Posted Date: February 7th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1281533/v1>

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Abstract

Purpose: To investigate multi-mode imaging characteristics for understanding the natural prognosis of large avascular retinal pigment epithelium detachment (aPED) in macular area.

Methods: We retrospectively analyzed patients diagnosed with aPED at Beijing Tongren Hospital Affiliated to Capital Medical University from January 2010 to June 2021. Patients with aPED maximum diameter greater than 1500 μm underwent best-corrected visual acuity (BCVA), fundus color photography, spontaneous fluorescence, infrared photography, FFA, ICGA, and OCT tests. Based on aPED characteristics, patients were divided into serous or drusenoid PED. In addition, the imaging characteristics for different types of large aPED were explored for its natural diagnosis.

Results: A total of 64 eyes of 50 cases with large aPED were recruited. 21 males and 29 females with an average age of 64.31 ± 6.38 years. The recruited population included 14 cases with the binocular disease, whereas 13 and 51 eyes had serous and drusenoid PED, respectively. Eight eyes (61.54%) of serous PED patients had drusen. Drusenoid PED patients had drusen in 47 eyes (92.17%). The OCT of serous PED patients showed large PED with uniform low reflection and RPE hyperplasia ($n=2$ eyes). In contrast, the OCT of drusenoid PED patients showed some uneven, slightly high, or high reflection and RPE hyperplasia in all the eyes. In addition, 46 eyes were accompanied by the subretinal fluid (SRF) (90.20%), 28 eyes developed hyperreflective foci between retinal layers (54.90%), and 3 eyes had inner retinal capsules (5.88%). No abnormal blood flow signal was detected in OCTA. The independent t-test showed no significant differences in the general conditions between the two groups, including age, BCVA, PED bottom diameter, and PED height. A total of 19 eyes of 16 cases were followed up, with an average follow-up time of 21.56 ± 18.85 months. Out of these 19 eyes, 12 eyes developed enlarged PED bottom diameter (63.16%), 5 eyes had partial or entire geographic atrophy (26.32%), 1 eye had RPE laceration (5.26%) and 1 eye had no changes (5.26%). However, no case developed into vascular PED (vPED).

Conclusions: Multi-mode imaging provided imaging events, contributing to a more accurate diagnosis of aPED. Different types of aPED might be the different stages of same disease, need close observation, however, the natural course of disease shifted to geographic atrophy.

Trial registration: Retrospective case series study, not applicable.

Introduction

Retinal pigment epithelium detachment (PED) is the separation between the retinal segment epithelium (RPE) and the inner collagen layer of the bruch membrane, which is a typical feature of dry and wet age-related macular degeneration as firstly described by Gass in 1966 [1]. Based on neovascularization, PED can be divided into vascular and avascular PED (aPED). The introduction of anti-VEGF drugs has revolutionized the vPED treatment, with the marked improvement in patient's vision [2–4]. However, the early diagnosis and treatment of aPED remain controversial [5–6]. Moreover, conflicting opinions exist on the nature of large aPED. Therefore, our study has summarized and analyzed the multi-mode imaging

features of large aPED in recent 10 years. We recorded the changes in some patients and investigated the imaging characteristics and natural prognosis of aPED.

Methods

Patients

We retrospectively investigated 50 aPED patients (64 eyes) diagnosed based on the FFA+ICGA+OCT findings at Beijing Tongren Hospital Affiliated with Capital Medical University from January 2010 to June 2021.

Inclusion criteria: Age > 50 years old, subfoveal aPED as verified by the fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA). All recruited cases had best-corrected visual acuity (BCVA), color fundus photography, spontaneous fluorescence, infrared photography, FFA, ICGA, and OCT tests done. Besides, we measured the maximum diameter of PED whenever the maximum diameter was greater than 1500 μm . For the comparison, the vision of all patients was converted to logMAR [7].

Exclusion criteria: (1) maximum diameter of PED < 1500 μm ; (2) PED with neovascular components; (3) subretinal hemorrhage, macular retinal hemorrhage and edema caused by any other reason; (4) foveal fibrosis; (5) failure to obtain clear images due to any other reasons, such as refractive opacity caused by cataract, corneal disease or vitreous hemorrhage; (6) history of vitrectomy.

This study followed the Helsinki Declaration, and the ethics committee approved the protocol of Beijing Tongren Hospital Affiliated with Capital Medical University. Furthermore, since the collected data were obtained as routine, the ethics committee approved to exempt the study subjects from informed consent

Methods

For recruited patients in this retrospective analysis, all imaging examinations were independently evaluated by the two experienced retina experts. Based on the imaging characteristics, aPED was further divided into serous and drusenoid PED. First, followed by analyzing the characteristics of FA and ICGA, we investigated the imaging features of different aPED, including the color fundus image, infrared photography, and spontaneous fluorescence. Next, we measured the height and diameter of aPED in the OCT test and assessed for the presence of subretinal fluid, inter-retinal fluid in the outer retina, and RPE. Finally, the changes in PED during the follow-up period were also analyzed.

Statistical analysis

SPSS17.0 was used for the analysis of data. The data were expressed in $\bar{x} \pm s$. The PED diameter measured by different detection methods, BCVA and PED height, and PED diameter measured by OCT among groups were analyzed using independent and paired samples t-test. The $p < 0.05$ was considered statistically significant.

Results

General information

50 cases (64 eyes) recruited in this analysis had large aPED in the macular area. There were 21 males and 29 females, with an average age of 64.31 ± 6.38 years. Out of the total, 14 cases had binocular diseases (44.0%), all of which had largely aPED. Besides, 5 cases had aPED in the contralateral eye with a diameter less than $1500 \mu\text{m}$. Whereas 1 case developed geographic atrophy, and 2 cases had polypoid chorioretinopathy (PCV) in the contralateral eye. Additionally, 21 cases (25 eyes) received OCTA, and 19 eyes of 16 cases were followed up with an average follow-up time of 21.56 ± 18.85 months (see Table 1).

Table 1
Patient's Basic Characteristics

Total number of eyes (n)	64
Total number of patients (n)	50
Both eyes of large avascular PED	14
Small avascular PED of the fellow eye	5
Geographic Atrophy of the fellow eye	1
PCV of the fellow eye	2
Male: Female	21: 29
Mean age (y)	64.31 ± 6.38
LogMar VA	0.57 ± 0.38
Follow-up time (m, 16 cases)	21.56 ± 18.85
Types of avascular PED, n (%)	
Serous PED	13 (20.31%)
Drusenoid PED	51 (79.69%)

Imaging Characteristics Of Serous Ped

A total of 13 eyes had serous PED, where the colors images showed a transparent PED, without yellow changes. Whereas the 8 eyes had drusen (61.54%). The infrared image revealed that PED had slightly low fluorescence, with its outer ring being slightly high fluorescence. In spontaneous fluorescence, PED had slightly high spontaneous fluorescence, however, its outer ring was in low spontaneous fluorescence without the inclusion of high spontaneous fluorescence. The FFA images revealed low fluorescence for PED in the venous phase, whereas the gradual fluorescence accumulation in PED showed high fluorescence excluding the inside low fluorescence. ICGA also showed low fluorescence PED in an early

stage; however, in the late stage, low fluorescence was observed without the inclusion of even lower fluorescence and high fluorescence. Further, OCT images showed large PED with uniform low reflection, whereas the RPE hyperplasia and accumulation could be seen in two eyes. Besides, collapse of RPE was seen in one eye. However, no abnormal blood flow signal was observed in the OCTA (see Table 2 and Fig. 1).

Table 2
Multi-mode imaging characteristics of different types of aPED, summary of clinical and imaging characteristics

characteristics of PED	Serous PED (13)	Drusenoid PED (51)
Fundoscopy	Transparent PED	Yellow-white PED
Complicated drusen	8 (61.54%)	47 (92.17%)
Infrared image	PED had slightly low fluorescence, and its outer ring had a slightly high fluorescence	PED was in low fluorescence, with inside flaky or radial high fluorescence
Fundus autofluorescence	PED had slightly high spontaneous fluorescence with low in outer ring.	PED showed slightly high spontaneous fluorescence with inside more high fluorescence.
FFA	PED no leak	PED no leak with inside low fluorescence
ICGA	No hot spots	No hot spots with inside low fluorescence
OCT	large PED with uniform low reflection	large, bulged PED with some uneven, slightly high, or high reflection
SRF on OCT	11 (84.62%)	46 (90.20%)
Hyperplasia of RPE	2 (15.38%)	51 (100%)
Hyperreflective foci	0 (0%)	28 (54.90%)
Cystic cavity	0 (0%)	3 (5.88%)
Collapse of RPE	1 (9.09%)	11 (21.57%)

Imaging Characteristics Of Drusenoid Ped

A total of 51 eyes had drusenoid PED. The color image revealed a PED interior with yellow changes located at the edge of the center of the PED. Meanwhile, some cases showed pigmented changes, and 47 eyes (92.17%) had drusen. The infrared image showed low fluorescence PED, including inside flaky or

radial high fluorescence. Spontaneous fluorescence showed a slightly high spontaneous fluorescence PED. The high spontaneous fluorescence inside corresponded to the infrared image high fluorescence, revealing the same as the high spontaneous fluorescence with the nearly identical shape. FFA showed low fluorescence in PED at the venous phase. The corresponding low fluorescence inside the flake or radial high spontaneous fluorescence had lower shielding fluorescence with nearly the same shape but without the leakage. The fluorescence accumulation in PED gradually showed high fluorescence with persisted low fluorescence inside. The low-intensity fluorescence in PED was more significant compared with the high fluorescence. At the early stage of ICGA, PED had low fluorescence with the inclusion of even lower fluorescence. In the late stage, PED continued to show low fluorescence without any inside hot spots. The OCT images showed large, bulged PED with uneven, slightly high, or high reflection, whereas the RPE hyperplasmia and accumulation could be seen in all eyes. Overall, there were 46 eyes with SRF (90.20%), 28 eyes with hyperreflexive foci between retinal layers (54.90%), 3 eyes with inner retinal capsules (5.88%), and 11eyes with collapse of RPE (21.57%). No abnormal blood flow signal was seen in OCTA of drusenoid PED (see Table 2 and Fig. 2).

Statistical Analysis Of Serous And Drusenoid Ped

Serous and drusenoid PED LogMar vision were 0.47 ± 0.35 and 0.60 ± 0.38 , respectively. An independent sample t-test was conducted between the two groups that showed no statistical significance difference ($t=-1.173$, $P=0.254$). The size of PED measured by the infrared image was $3320.78\pm949.60\text{ }\mu\text{m}$, with the bottom diameter of PED of $3266.61\pm989.03\text{ }\mu\text{m}$ as measured by the OCT. In PED measured by infrared image and OCT, no significant difference using the paired t-test showed ($t = 1.299$, $P = 0.199$). Therefore, OCT was used to measure PED in the current study. The bottom diameter and height of serous PED measured by OCT were 3192.62 ± 1202.82 and $493.15\pm200.66\text{ }\mu\text{m}$, respectively. The bottom diameter and height of drusenoid PED were 3285.73 ± 939.91 and $478.16\pm176.98\text{ }\mu\text{m}$, respectively. An independent sample t-test conducted between the two groups showed no significant differences ($t=-0.262$ and 0.246 , $P=0.796$ and 0.808) (see Table 3).

Table 3
Data analysis of two different types of aPED

	Serous PED (13)	Drusenoid PED (51)	t-value	p-value
Mean age	63.31±7.57	64.82±6.09	-0.669	0.513
LogMar VA	0.47±0.35	0.60±0.38	-1.173	0.254
IR PED diameter	3344.00±1090.94 μm	3314.86±922.16 μm	0.089	0.930
OCT PED diameter	3192.62±1202.82 μm	3285.73±939.91 μm	-0.262	0.796
OCT PED height	493.15±200.66 μm	478.16±176.98 μm	0.246	0.808

Follow Up

19 eyes were followed up, with an average of 21.56 ± 18.85 months. Among them, the bottom diameter of PED was enlarged in 12 eyes (63.16%), partial or total geographic atrophy was seen in 5 eyes (26.32%), 1 eye (5.26%) had RPE laceration, whereas no significant change in 1 eye (5.26%) and no neovascularization was observed. In a typical case with the enlarged PED, high fluorescence on the infrared image did not increase, except for the expansion of low fluorescence from the peripheral serous (Fig. 3). However, while shifting into geographic atrophy, some cases absorbed yellow substances or developed brighter crystalline substances (Fig. 4)

Discussion

PED is defined as the separation between the RPE and the inner collagen layer of the bruch membrane, which is an important sign for age-related macular degeneration. After anti-VEGF treatment, the vPED patient's condition and vision can be partly controlled and improved. However, aPED early diagnosis or treatment is still controversial. The relationship or the different stages similarities between serous PED and drusenoid PED has not been reported. Therefore, this study summarized and analyzed the multi-mode imaging characteristics of large aPED in the past 10 years for providing the natural disease changes and improved basis for aPED diagnosis.

It has been demonstrated that FA, ICGA, and OCT could confirm the diagnosis of aPED. The FFA showed no vascular leakage, and ICGA revealed no plaque and hotspots [5, 6, 8]. When the aPED is a dome with a low reflection in OCT, accompanied by the fluorescence accumulation in FA but low fluorescence in ICGA, it is generally defined as the serous PED. If in clinical fundus examination, the focus of aPED appears yellow with high reflection, accompanied with staining/accumulation in FA and low fluorescence in ICGA, it is defined as drusenoid PED. The selection and classification are aPED based on the criteria mentioned above. Finally, 64 aPED patients with a diameter greater than 1500 μm , including 13 serous PED cases and 51 drusenoid PED cases, were included in the study. Karadimas *et al.* [9] reported that drusenoid PED spontaneous fluorescence showed high or low fluorescence. Our results showed that, in drusenoid PED, spontaneous fluorescence was slightly high spontaneous fluorescence, with the flake or radial high fluorescence inside. The infrared images showed low fluorescence PED, including flake or radial high fluorescence inside, corresponding to the spontaneous high fluorescence. However, no leakage was found either in FFA or ICGA, but lower fluorescence corresponding to high spontaneous fluorescence could be seen. Moreover, no flake or radial high fluorescence was observed in the serous PED. The increased spontaneous short-wavelength fluorescence originates from lipofuscin and melanin lipofuscin. It may also arise from the liquid under RPE. However, a high infrared fluorescence signal originates from melanin and melanin lipofuscin [9–10]. Our results showed that high spontaneous fluorescence in drusenoid PED represented significant RPE changes in PED, however, no significant moving and accumulation of RPE cells was observed in serous PED. Further, the OCT results of all drusenoid PED showed significant RPE accumulation, which corresponded to the high fluorescence in the infrared image and spontaneous fluorescence, representing the increased lipofuscin and melanin activity. Meanwhile,

low fluorescence in FFA and ICGA might have occurred due to the RPE pigment masking. A slight accumulation of RPE was seen in 2 eyes of serous PED patients, which was not reflected in other imaging images.

What is the pathogenesis of serous PED and drusenoid PED? Is there a correlation between the serous PED and drusenoid PED? The common mechanism of PED is the occurrence of the lesion, based on the pathological process [11–13]. It is the condition where the bruch membrane thickens gradually with age, leading to the accumulation of lipids and other metabolites, increased hydrophobicity, and decreased hydraulic conductivity. This condition causes loops in the barrier in terms of RPE pump function draining to choroidal capillaries, followed by RPE separation. It is also considered the pathogenesis of serous PED [11, 12]. Another mechanism is the accumulation of residual bodies in RPE cells, resulting in drusenoid formation and separation of RPE from the bruch membrane. Some scholars suggested that drusenoid PED resulted from the large drusenoid fusion [13–15]. Since there are similarities in the pathogenesis, do serous PED and drusenoid PED represent the different stages of the disease? Therefore, we analyzed the general features of serous and drusenoid PED, while no significant differences in age, vision, PED bottom diameter, and PED height was observed between the two groups. There were 8 eyes with drusenoid in serous PED patients (61.54%). However, not all drusenoid patients had drusen, despite 47 eyes with drusenoid (92.17%), collapse of RPE could be seen in 11 eyes of drusenoid PED (21.57%). There were serous PED cases with slight RPE accumulation and collapse of RPE, as observed in the OCT. Additionally, in the follow-up cases, a drusenoid PED case was enlarged from the peripheral serous, while the increased high fluorescence was not found in the infrared and spontaneous fluorescence images. Moreover, increased RPE accumulation was not seen on OCT. Analyzing the above findings, we speculated that large serous PED might represent early stage of drusenoid PED, but without significant RPE hyperplasia and accumulation. This observation needed to be further verified by the large serous PED samples with the long-term follow-up.

The natural outcome of aPED patients was not good. Our study found that 28 eyes of drusenoid PED had hyper reflexive foci between the retinal layers (54.90%), whereas the 3 eyes had inner retinal capsules (5.88%) and 11 eyes had collapse of RPE (21.57%). After hyperplasia, part of RPE dissociated into the retinal layer or stimulated the microglia hyperplasia, resulting in hyper reflexive foci [16]. Additionally, the inner retinal capsule represented the process of chronic hypoxia of the disease, resulting in cystic degeneration rather than vascular leakage, which is caused by the destruction of internal barrier function. The absence of vascular leakage could be confirmed by the absence of fluorescein leakage in FFA. Large PED caused the high separation between RPE and bruch membrane. Due to this, RPE and retina failed to obtain the nutrients from the choroidal capillaries, affecting the metabolism of RPE and outer retina, eventually leading to RPE and outer retina atrophy which can also explain the collapse of RPE [17–20]. Studies of age-related eye diseases^[14,21] revealed that 42% of the 282 eyes with drusenoid aPED developed advanced AMD, accompanied by central geographic atrophy (19%) or nAMD (23%). In another study [6], 12 drusenoid aPED eyes received long-term follow-up, however all patients developed advanced AMD, whereas the 10-year incidence of central geographic atrophy was 75%. In our study, 19 eyes were

followed up, where 12 eyes had enlarged PED bottom diameter (63.16%), 5 eyes had partial or total geographic atrophy (26.32%), 1 eye had RPE laceration (5.26%) without vascular age-related macular degeneration. Our findings differed slightly from the previous reports [14, 21, 22] related to the limited follow-up cases and insufficient follow-up time. It gives insight that another outcome of drusenoid PED is RPE laceration. In our follow-up cases, an interesting phenomenon was encountered: crystal-like substances appeared in the transformation process to geographic atrophy, corresponding to hyperreflexia in the OCT images. It is speculated that hypoxia and further deposition of metabolites might have caused the further calcification and cholesterol crystal of RPE cells and bruch membrane during the development of the disease [16, 23, 24].

There were some limitations to this study. First, it was a retrospective study and might have selective bias. Second, the number of follow-up cases was limited, along with the short follow-up time. Therefore, the long-term natural disease changes could not be analyzed. Third, the changes of aPED were not dynamically recorded during the follow-up. Fourth, aPED patients did not receive the intervention treatment. Therefore, more accurate conclusions need to be drawn and verified by large samples. Therefore, it is necessary to include more samples, increase the follow-up frequency and the follow-up time. Additionally, intervention measures should be performed to explore the prognosis of aPED.

In conclusion, multi-mode imaging provides more robust visual evidence for aPED diagnosis. Two different types of aPED might have different stages of the same disease and therefore need to be closely observed. The natural course of disease tends to change the geographic atrophy, which also needs to be explored for providing a basic reference point for further intervention and treatment.

Abbreviations

PED: pigment epithelial detachment; aPED: avascular pigment epithelial detachment; vPED: vascular pigment epithelial detachment; nAMD: neovascularized AMD; BCVA: best-corrected visual acuity; LogMAR: Logarithm of the minimum angle of resolution; SRF: subretinal fluid

Declarations

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Authors' contributions

BM, YL, YJY, WL analyzed and interpreted the patient data. BM was major contributors in writing the manuscript. BM and WL were critical revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of the Beijing Tongren Hospital. Due to the retrospective nature of this study, the informed consent from individual patient was waived by the Ethical Committee of the Beijing Tongren Hospital in this study. This study complied with the guidelines of the Helsinki.

Consent for publication

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Acknowledgements

Not applicable.

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Figures

Figure 1

The multi-mode imaging of a typical serous PED case: A color image, serous PED was in the macular area without yellow changes, accompanied by the drusen; B infrared image; C spontaneous fluorescence image; D 30-second FFA+ICGA image; E 16-minute FFA+ICGA image; F OCT image, there was low reflection under PED with slight RPE hyperplasia.

Figure 2

The multi-mode imaging of a typical drusenoid PED case: A color image, drusenoid PED was in the macular area with inside yellow changes; B infrared image, several flaky high fluorescence could be found in low fluorescence; C spontaneous fluorescence image, PED was in slightly high spontaneous fluorescence, which was corresponding to the infrared image; D 30-second FFA image in the venous phase; E 10-minute FFA image in the late stage; F ICGA image in an early stage; G ICGA image in the late stage without hot spots inside PED; H OCT image, there was uneven high reflection with RPE hyperplasia.

Figure 3

The follow-up of a typical drusenoid PED case. A, B, C color image, infrared image and spontaneous fluorescence image at baseline; D, E, F color image, infrared image and spontaneous fluorescence image after 9 months of follow-up; PED was enlarged from the peripheral serous, with no increase in high fluorescence on the infrared image, except the expansion of low fluorescence; G, H OCT images at baseline and after 9 months of follow-up, PED was enlarged.

Figure 4

The follow-up of a typical drusenoid PED case. A, B, C color image, infrared image and spontaneous fluorescence image at baseline; D, E, F color image, infrared image and spontaneous fluorescence image after 26 months of follow-up, geographic atrophy could be found; G, H OCT images at baseline and after 26 months of follow-up, PED was enlarged, geographic atrophy could be found.

Supplementary Files

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