Clinical features of cases with retinal pigment epithelium aperture

Akie Yoshinaga a,b, Kohei Ueda a, Ryo Terao a, Keiko Azuma a, Tatsuya Inoue b,c, Ryo Obata a,*

a Department of Ophthalmology, The University of Tokyo Hospital, Tokyo, Japan
b Department of Ophthalmology, Saitama Red Cross Hospital, Saitama, Japan
c Department of Ophthalmology, Yokohama City University Medical Center, Kanagawa, Japan

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ABSTRACT

Purpose: To report the clinical findings of the patients with retinal pigment epithelium (RPE) aperture secondary to age-related macular degeneration (AMD).

Methods: A retrospective data analysis was conducted of patients at the University of Tokyo Hospital eye clinic, from the year September 1st, 2012 to 2019. Review of the medical records of patients with RPE aperture accompanied by AMD was performed. We investigated age, best-corrected visual acuity (BCVA), images of spectral domain optical coherence tomography, short-wave fundus autofluorescence (FAF), fluorescein angiography (FA), indocyanine green angiography, and retinal sensitivity measured with microperimetry. The change in visual acuity or the area of the aperture during the follow-up period was analyzed.

Results: Five eyes of 5 patients (4 men, one woman) were included in the analysis. The mean age at presentation was 78.6 ± 9.1 years. The average length of follow-up was 23.6 ± 17.9 months. The RPE apertures appeared as round, either at the apex or at the base of PED, with no evidence of accompanying CNV but subretinal detachment (SRD) above the aperture. On FAF, the apertures appeared as sharply demarcated round areas of hypofluorescence. The FA revealed sharply demarcated round areas of window defects in the early and mid-phase with leakage in the late phase corresponding to SRD. The area of apertures enlarged during the follow-up period. Mean BCVA got worse from 0.20 logMAR at the initial presentation to 0.39 logMAR at the last visit. The retinal sensitivity was reduced but partly preserved above the area of aperture.

Conclusions and importance: RPE aperture was found in some patients with drusenoid PED secondary to AMD. It enlarged during follow-up. Visual acuity was declined. Retinal sensitivity was decreased but partly preserved.

1. Introduction

Retinal pigment epithelium detachment (PED) is a prominent feature of many chorio-retinal disease processes, including central serous chorioretinopathy (CSCR), inflammatory, neoplastic, iatrogenic etiologies, and neovascular/nonneovascular age-related macular degeneration (AMD). Longstanding PEDs cause thinning in the RPE on OCT, leading to expected complications during follow-up. Patients with PED from nonneovascular or dry form of AMD shows relatively more favorable prognosis than those with neovascular AMD. PEDs with CNV may develop retinal pigment epithelium (RPE) tears, typically at the edge of attached and detached RPE, where the PED is most vulnerable to hydrostatic forces. RPE tears result in loss of photoreceptors with the development of fibrous tissue and enlargement of the RPE defects, leading to remarkable decrease of visual acuity.

Recently, RPE aperture was reported as a new finding associated with PED. RPE aperture was characterized by round RPE defect accompanying with PED. It was found in several diseases including AMD, adult-onset foveomacular vitelliform dystrophy, and chronic central serous chorioretinopathy. RPE aperture in AMD should be distinguished by typical RPE tears and thought to develop in the evolution of nonneovascular AMD. There have been few reports on RPE aperture, making the demography or pathogenesis of this finding still unclear. Additionally, retinal function other than visual acuity has not been reported to the best of our knowledge. Herein, we reported the clinical characteristics of Asian patients with RPE aperture associated with AMD, and analyzed in some subjects their retinal function evaluated with fundus microperimetry.

2. Materials and methods

A retrospective data analysis was conducted of patients at the University of Tokyo Hospital eye clinic, from the year September 1st, 2012 to 2019. Review of the medical records of patients with RPE aperture accompanied by AMD was performed. We investigated age, best-corrected visual acuity (BCVA), images of spectral domain optical coherence tomography, short-wave fundus autofluorescence (FAF), fluorescein angiography (FA), indocyanine green angiography, and retinal sensitivity measured with microperimetry. The change in visual acuity or the area of the aperture during the follow-up period was analyzed.

Results: Five eyes of 5 patients (4 men, one woman) were included in the analysis. The mean age at presentation was 78.6 ± 9.1 years. The average length of follow-up was 23.6 ± 17.9 months. The RPE apertures appeared as round, either at the apex or at the base of PED, with no evidence of accompanying CNV but subretinal detachment (SRD) above the aperture. On FAF, the apertures appeared as sharply demarcated round areas of hypofluorescence. The FA revealed sharply demarcated round areas of window defects in the early and mid-phase with leakage in the late phase corresponding to SRD. The area of apertures enlarged during the follow-up period. Mean BCVA got worse from 0.20 logMAR at the initial presentation to 0.39 logMAR at the last visit. The retinal sensitivity was reduced but partly preserved above the area of aperture.

Conclusions and importance: RPE aperture was found in some patients with drusenoid PED secondary to AMD. It enlarged during follow-up. Visual acuity was declined. Retinal sensitivity was decreased but partly preserved.

* Corresponding author. Department of Ophthalmology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, Tokyo, 113-8655, Japan.
E-mail address: robata-gky@umin.ac.jp (R. Obata).

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University of Tokyo Hospital eye clinic, from the year September 1st, 2012 to 2019. Review of the medical records of 5 eyes of 5 patients with RPE aperture associated with AMD was performed. All patients underwent a complete ophthalmic examination routinely in every 2-month visits, including best-corrected visual acuity (BCVA), color fundus photography, dilated ophthalmoscopy, spectral domain optical coherence tomography (SD-OCT, Spectralis®, Heidelberg Engineering, Heidelberg, Germany). Fundus autofluorescent imaging using a short-wave length (SW-AF; 488 nm) light source (Spectralis HRA®, Heidelberg Engineering, Heidelberg, Germany). Indocyanine-green angiography (ICGA) and fluorescein angiography (FA) were performed using Spectralis® HRA. In some patients, retinal sensitivity was measured with fundus-monitoring microperimetry (MP-3®, Nidek Co, Japan). The MP-3 measurement was based on a 4–2 full threshold staircase strategy. The stimulus dynamic range was between 0 and 34 dB. Twenty-five stimulus points were examined, covering 8°. Measurements were performed using the standard Goldmann III stimulus size. After completion of sensitivity testing, a color fundus image with the superimposed sensitivity values was exported from the device. Mean sensitivity values at the total area, the aperture area, and the non-aperture area were calculated.

3. Results

3.1. Representative cases

3.1.1. Case 1

An 81-year-old woman presented with decreased vision in her both eyes. Her diagnosis of the referring doctor was drusenoid PED. She had received 12 times of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy (3 ranibizumab, 9 aflibercept) before the referral to our clinic. The BCVA was 0.30 logMAR in both eyes at initial visit to our clinic. The fundus showed grayish-white drusenoid PED at the center of the macula (Fig. 1a). Microperimetry testing showed that an aperture area had a decreased sensitivity (Fig. 1b). The OCT scans revealed PEDs with SRD, and apertures were seen (red arrow). We found the loss of external limiting membrane accompanied by outer retinal thinning, ellipsoid or interdigitation zone loss in some areas of the PED. FA (00:53) and ICGA (01:09) showed no evidence of any CNV. FAF showed sharply demarcated round apertures. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
3.1.2. Case 2
A 79-year-old men presented complaining of poor vision in both eyes. He was diagnosed as drusenoid PED secondary to AMD by the referring doctor. His BCVA in both eyes were 0.22 logMAR at initial visit. OCT showed a PED and an aperture in his left eye, no any SRDs (Fig. 2a). Microperimetry testing showed that an aperture area had a decreased sensitivity (Fig. 2b). FA (03:34) showed no evidence of CNV. FAF showed multiple hyperautofluorescent spots at the site of the PED (Fig. 2d). The patient received 3 times of anti-VEGF therapy (aflibercept). His VA was 0.52 logMAR at the last visit.

3.1.3. Case 3
An 89-year-old men presented with decreased vision in his left eye. His diagnosis of the referring doctor was drusenoid PED. The BCVA was 0.30 logMAR in his left eye at his first visit. FA and ICGA showed no evidence of any CNV. The SD-OCT revealed the RPE aperture with SRD. The BCVA dropped to 0.52 logMAR at the last visit.

3.1.4. Case 4
An 84-year-old men, noted a visual acuity decrease in the left eye. His diagnosis of the referring doctor was drusenoid PED. The BCVA was 0.05 logMAR in his left eye at first visit. FA and ICGA showed no evidence of any CNV. The SD-OCT revealed a central RPE-defect, SRF. FA and ICGA showed no definite evidence of a CNV.

3.1.5. Case 5
A 64-year-old men had decreased vision in his right eye and distortion. He was diagnosed as drusenoid PED secondary to AMD by the referring doctor. The BCVA was 0.15 at first visit in his right eye. FA and ICGA showed no evidence of any CNV, OCT showed the aperture.

In the present study, RPE apertures were identified in 5 eyes of 5 patients (4 men, one woman). All patients were Japanese. Clinical characteristics of 5 patients are shown in Table 1. Mean age was 78.6 ± 9.1 years at presentation, Mean BCVA at presentation was 0.20 ± 0.11 logMAR.

On SD-OCT, the RPE apertures appear as round, either at the apex or at the base of PED, with no CNV, and occurred with subretinal fluid (SRD) which considered as generated from aperture. RPE aperture was found with drusenoid PED. On FAF, RPE apertures appeared as sharply demarcated round areas of hypoautofluorescence (Fig. 1g). The FA and

### Table 1
Clinical characteristics of 5 patients (5 eyes) with AMD that developed RPE aperture.

| Case# | Age (years) | Gender | Follow-up period in our clinic (months) | IVT number of Anti-VEGF in our clinic | Findings in the Fellow eye |
|-------|-------------|--------|----------------------------------------|----------------------------------------|---------------------------|
| 1     | 81          | F      | 16                                     | 1* (aflibercept 1)                     | drusenoid PED             |
| 2     | 79          | M      | 18                                     | 3 (aflibercept 3)                      | drusenoid PED             |
| 3     | 89          | M      | 55                                     | 6 (ranibizumab 2)                      | fibrotic scar             |
| 4     | 84          | M      | 19                                     | 3 (aflibercept 3)                      | drusenoid PED             |
| 5     | 64          | M      | 10                                     | 0                                      |                           |
| Average | 78.6 ± 9.1 |        | 20.4 ± 9.2                             | 2.6 ± 2.3                              |

IVT; intravitreal therapy. VEGF; vascular endothelial growth factor. PED; pigment epithelial detachment. *Case 1 had undergone 12 IVT of anti-VEGF agents (3 ranibizumab and 9 aflibercept) before she was referred to our clinic. Mean age was 78.6 ± 9.1 years at presentation, Mean BCVA at presentation was 0.20 ± 0.11 logMAR.
ICGA revealed sharply demarcated round areas of window defects in the early, mid phases, with a leakage in the late phase corresponding to the subretinal fluid accumulation detected on OCT. One of the apertures of Case 1 and 2 was overlying the fovea, whereas in Case 3–5 they were at parafovea. The positional relation between RPE aperture and central fovea seemed to have little effect on BCVA decline. Findings suggesting pachychoroid such as dilation of choroidal vessels or choroidal vascular hyperpermeability in ICGA were not detected in all patients of the current case series.

Three of five subjects underwent retinal sensitivity measurement with microperimetry. Mean sensitivity values at the total area, the aperture area, and the non-aperture area were indicated in Table 2. Within the aperture area, mean retinal sensitivity was reduced compared with the non-aperture area (9 dB vs 18 dB, respectively), whereas each sensitivity was widely varied (from 19 dB to 0 dB at the aperture area and from 29 dB to 0 dB at the non-aperture area).

An average length of follow-up in our clinic was 23.6 ± 17.9 months. The change in visual acuity and anatomical findings are shown in Table 2. Mean BCVA got worse from 0.20 logMAR at the initial presentation to 0.30 logMAR at the last visit (p = 0.005). The RPE apertures significantly enlarged homogeneously (from mean 2.56 ± 2.40 to 3.45 ± 3.02 mm²; p = 0.028). PED maximal height on SD-OCT significantly increased from 143.2 ± 102.6 to 209.0 ± 145.0 μm (p = 0.047).

None of the included eyes showed evidence of CNV during the study period. 4 eyes with SRD had intravitreal anti-VEGF injections, but it did not work.

4. Discussion

In the present report, we studied the clinical findings of five Japanese patients with RPE aperture accompanied by PED due to AMD. It was sharply demarcated round areas of hyperscience in FAF. No patients had CNV. The area of the aperture enlarged during follow-up. BCVA was impaired at first visit and worsened until the last visit. Retinal sensitivity, which have been no report to the best of our knowledge, was also reduced but partly preserved with wide variance.

Mean age was older than previously reported. Furthermore, mean BCVA was better than the previous report by Querques et al. (0.62 logMAR). The difference in the age and the visual acuity between the previous report and the present case series might result from the different ethnicity. Because prevalence rate of nonneovascular AMD is different between Europeans and Asian, the age of onset and course of visual decline may be different between Europeans and Asian.

The shape and location of the RPE aperture was comparable to the previous report. The reason for the development of RPE aperture in patient with drusenoid PED secondary to AMD has been uncertain. Different from RPE tears, no rippling or retraction of the RPE was found at the sites of aperture. The RPE apertures enlarge homogeneously, whereas RPE tears typically tend to stay stable with no enlargement.

Thus, RPE aperture should be considered to be a distinct finding from typical RPE tear. Inferentially, once RPE resections make tears, defect areas remain stable, whereas apertures enlarge as PED’s changing. Of note, RPE aperture is found mainly in patients with drusenoid PED. Thus, the development and progression of RPE aperture in patients with AMD can be the result of RPE degeneration during the natural course of drusenoid PED.

Mean BCVA got worse during the follow-up period. Querques G et al. noted that mean BCVA significantly decreased from 0.62 logMAR to 0.82 logMAR. Attenuation of overlying photoreceptor cells on drusenoid PED was documented in histopathological studies. It was also consistent with the findings that outer retinal atrophy was suggested in some areas above the PED of our cases. Because all patients in the present study showed drusenoid PED at/around the aperture, it is reasonable to consider that visual acuity significantly reduced in these eyes. However, the visual decline is not as critical as eyes with advanced AMD. Previous report showed that some patients with RPE aperture preserved relatively good visual acuity. Of note, some patients with RPE tear also preserved good visual acuity. The reason was uncertain, but some authors speculated that photoreceptors would be able to, if partly, survive without normal RPE. Further large-scale and longer-term study will be essential to conclude, but photoreceptor atrophy induced by selective RPE defect might not be as critical as more serve type of degeneration such as geographic atrophy.

In the current analysis, retinal sensitivity was evaluated by microperimetry in three patients. Within the aperture area, mean retinal sensitivity was reduced compared with the non-aperture area, but each sensitivity showed wide variance. To the best of our knowledge, there have been no report on retinal sensitivity in patients with RPE aperture. According to the previous reports assessing visual acuity, Querques et al. reported decreased visual acuity in the patients with aperture, while Giannakaki-Zemmermann et al. showed some patients with aperture preserving good visual acuity. The results of the current case series suggested that impairment of retinal function might also be varied individually. The detailed mechanism of this variable retinal dysfunction was uncertain in the scope of the present study. However, it could be reasonable to suggest that measuring retinal sensitivity in addition to visual acuity could be helpful in assessing impairment of retinal function in the patients with RPE aperture secondary to AMD.

None of the included eyes showed evidence of CNV during the study period. 4 eyes with SRD underwent intravitreal anti-VEGF injections, but it did not work as previously reported. Some cases in the present report underwent intravitreal administration of aflibercept, while all patients in the previous report had ranibizumab injection. Considering that aflibercept has higher potency than ranibizumab, these results indicated that anti-VEGF treatment should not be appropriate for treating SRD in the eyes with RPE aperture.

The limitations of the current study were retrospective design, small case number. Further large-scale prospective could elucidate the link between the pathogenesis of RPE aperture secondary to AMD.

5. Conclusions

We described 5 cases with RPE aperture secondary to AMD, which is different from RPE tear. In aperture eyes, BCVA tend to reduce after
follow-up and retinal sensitivity is decreased with variance. There were few reports of apertures, thus more studies of imaging data and researches are needed to reveal pathogenesis and conditions of apertures.

**Patient consent**

Consent to publish this report was not obtained. This report does not contain any personal information that could identify the patient.

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**Authorship**

All authors attest that they meet the current ICMJE criteria for Authorship.

**Declaration of competing interest**

Ryo Obata, Santen Pharmaceutical Co., Ltd, Bayer Yakuhin, Ltd, Novartis Pharma K.K, TOMEY CORPORATION.

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