

Retinal pigment epithelial tears following treatment in neovascular age-related macular degeneration

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Received: 2014-08-12 Accepted: 2015-05-13

DOI:10.18240/ijo.2016.03.29

Chen ZQ, Ye PP, Fang XY. Retinal pigment epithelial tears following treatment in neovascular age-related macular degeneration. *Int J Ophthalmol* 2016;9(3):478–480

Dear sir,

I am Dr Zhi-Qing Chen, from the Department of Ophthalmology of the Second Affiliated Hospital of Zhejiang University in Hangzhou, Zhejiang Province, China. I write to present two cases of neovascular age-related macular degeneration (AMD) occurred retinal pigment epithelium (RPE) tears after different treatment.

RPE tear is a rare complication of neovascular AMD, especially in association with a large pigment epithelial detachment (PED) [1-3]. RPE tears may be spontaneous associated with neovascular AMD [4]. Recent evidence indicates that the rate of this complication may be increased after anti-vascular endothelial growth factor (anti-VEGF) therapy [5-7].

We present two cases of neovascular AMD occurred RPE tears, one after receiving intravitreal anti-VEGF therapy and the other one after photodynamic treatment (PDT). The risks of RPE tear should be discussed before treatment for neovascular AMD patients. Regular following is necessary, although the incidence is very low.

CASE 1

A 82-year-old woman presented with decreased vision in her left eye (Figure 1). The best-corrected visual acuity (BCVA) was 0.5 in her left eye at baseline. Fluorescence angiography (FA) showed a fibrovascular PED and occult choroidal neovascularization (CNV). Indocyanine green angiography (ICGA) confirmed the occult CNV. Optical coherence tomography (OCT) (Carl zeiss, Cirrus HD-OCT4000, Germany) showed a serous retinal detachment and a

fibrovascular PED with the height of 408 μm . She was diagnosed with occult neovascular AMD associated with PED. After 15d of the first injection of intravitreal ranibizumab (0.5 mg/0.05 mL), a grade 1 RPE tear formed at the junction of the attached and detached RPE in the subfovea. One month later, the BCVA decreased to 0.2. RPE folded and high fluorescence with irregular edge covered fluorescent pigment was seen in FA. An obvious defect of the RPE and a focal disruption of the RPE corresponding to the tear seen on OCT.

CASE 2

A 64-year-old man had decreased vision in his right eye and distortion (Figure 2). His BCVA was 0.06. Right eye had a huge PED. FA and ICGA showed scattered clusters of mottled strong fluorescence in early phase and dye leakage in late phase. OCT showed that the height of PED was 1128 μm . The patient received photodynamic treatment (PDT) with the standards of the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) team and Verteporfin in photodynam in therapy (VIP) team method. After 1mo of PDT, a grade 4 RPE tear was formed. The BCVA decreased to 0.02. FA illustrated a large escentric area of transmission hyperfluorescence bigger than l-disk diameter corresponding to the area of absent RPE adjacent to an area of blocking hypofluorescence corresponding to the area of redundant RPE. OCT illustrated focal disruption in the RPE layer and a large area of RPE loss also be appreciated. The redundant RPE took on a dome-shaped configuration and OCT confirmed the presence of the RPE tear.

The prognosis of RPE tear had a strong correlation with the grade and the anatomical location. In 2010, Sarraf *et al* [8] introduced a new grading system for RPE tears. They classify RPE tears based on the longest linear diameter in the vector direction of the tear and defined 4 grade tears. Higher grade tears were larger with a worse prognosis. The RPE tear in the first patient located in the subfovea though it was smaller than 200 μm . The tear in the second one was evaluated as grade 4. So they both had poor visual acuity.

The reported incidence of RPE tears in the literature spans a broad range, from 1.8% to 27%, in both natural history and interventional series [9]. Recent several reports [5-7] indicates that the rate of this complication may be increased, or alternatively accelerated, after anti-VEGF therapy. However, as studied in anti-VEGF antibody for the treatment of

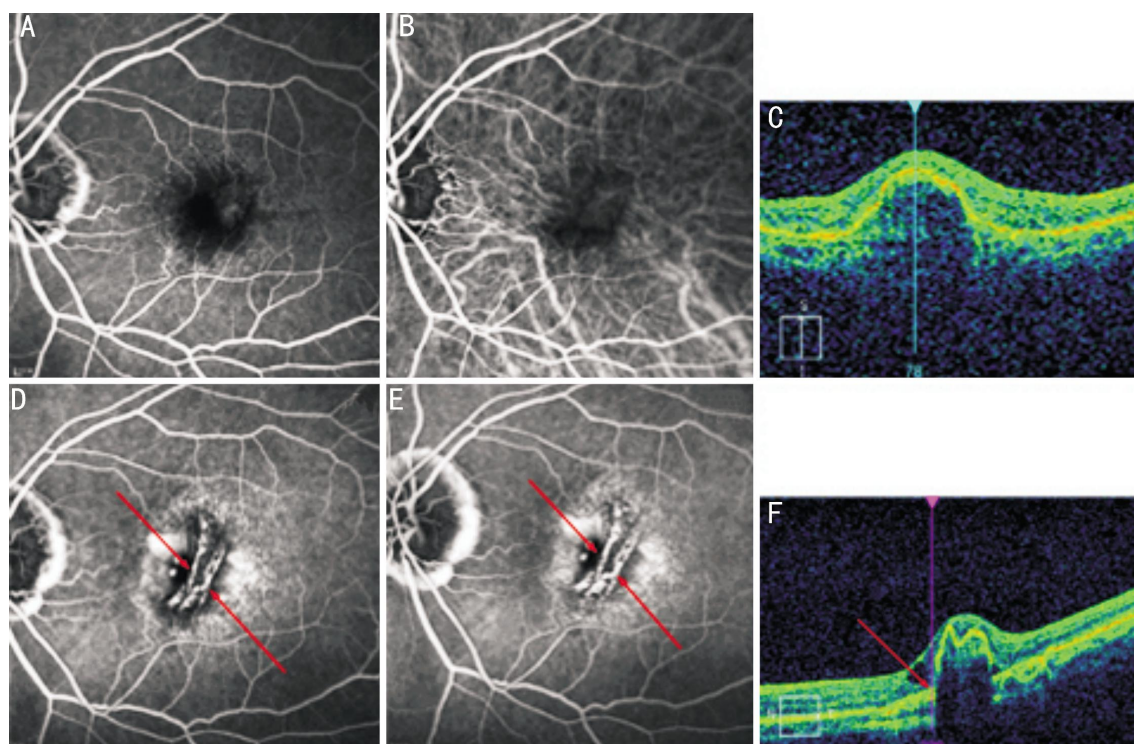


Figure 1 Fundus angiography and OCT results of case 1 A: FA showed hyperfluorescence in the subfovea; B: ICGA confirmed the occult CNV; C: OCT showed fibrovascular PED; D: FA showed high fluorescence with irregular edge of the RPE; E: ICGA confirmed the RPE tear; F: OCT showed a focal disruption of the RPE (arrow).

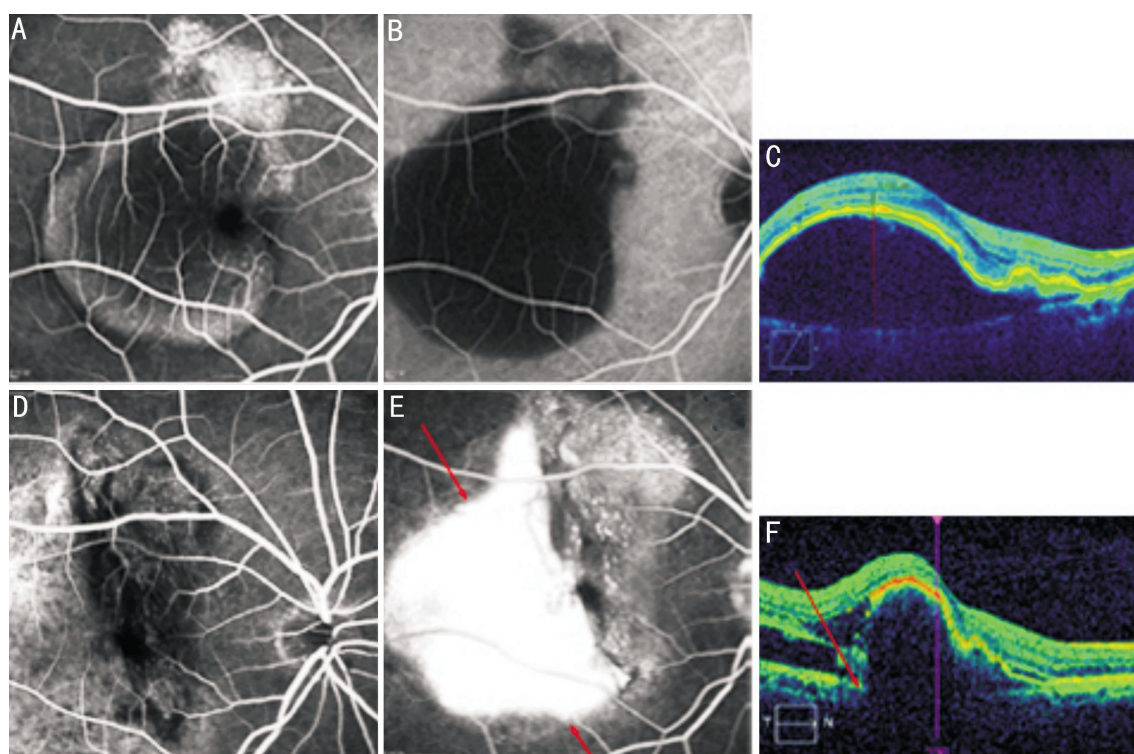


Figure 2 Fundus angiography and OCT results of case 2 A: FA showed scattered clusters of hyper-fluorescence in early phase; B: ICGA showed large area of hypo-fluorescence of PED; C: OCT showed huge PED; D: FA showed hypo-fluorescence of redundant RPE (early phase); E: FA illustrated a large escentric hyper-fluorescence of absent RPE (late phase); F: A dome-shaped configuration in OCT of the RPE tear.

predominantly classic choroidal neovascularization in age-related macular degeneration (ANCHOR), minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular age-related macular

degeneration (MARINA), and a phase IIIb, multicenter, randomized, double-masked, sham injection-controlled study of the efficacy and safety of ranibizumab (PIER) trials, no statistically significant differences in the incidence of RPE

tears within a 2-year treatment period were observed in patients who received ranibizumab (0.5 or 0.3 mg) versus control treatment, although most RPE tears with ranibizumab injection occurred within 3mo of initiating treatment^[10].

Various mechanisms have been proposed for the development of RPE tears. Gass^[11] and Krishan *et al*^[12] proposed that leakage from sub-RPE CNV could increase hydrostatic pressure sufficient to tear the RPE. Bird^[13] implicated the RPE pumping mechanism as a major contributor to fluid accumulation within a PED and to the development of an RPE tear secondary to hydrostatic forces. In addition to hydrostatic stresses, dynamic underlying CNV membranes may contract and exert significant tangential forces on the posterior surface of the detached RPE^[14]. Thermal contraction of CNV in the setting of laser photocoagulation was later proposed as another mechanism of tearing^[15]. PDT alone has been shown to be harmful as it increases the risk of RPE tear, hemorrhage and sudden visual acuity decrease^[16-17]. The increase in the magnitude of these forces after VEGF therapy contributes to the structural failure of the RPE monolayer^[18].

Increasing PED height strongly predicted the risk of RPE tearing and eyes without PED carried a 0.3% risk, 100 µm PEDs carried a 0.5% risk, and 600 µm PEDs carried a 14.8% risk of tearing following intravitreal bevacizumab^[2]. It is not only the height of the PED, but also the ratio between the height/width of PED is a risk factor^[19]. In addition to a large PED size serves as a predictor for RPE tears, Chan *et al*^[3] reported a stronger tendency to tear development in those PED lesions that show a smaller ratio of CNV size to PED size, especially smaller in fibrovascular PED lesions. In our two cases, we analyzed the risk factor of first case is occult CNV with fibrovascular PED. The second one is large and high PED. The height of PED was both higher than 400 µm in two cases.

Retreatment decisions are complex, given that fluid leakage may occur not only due to CNV activity, but also secondary to the absence of RPE, which functions to pump out fluid from the subretinal space. A judgment can be made whether the leakage is likely from CNV activity by comparing the location and the extent of the pre-tear CNV leakage with the post-tear angiogram. Several reports have suggested that persistent anti-VEGF therapy is important in eyes with RPE tears for continued suppression of neovascular activity. Anti-VEGF therapy appears safe in eyes with RPE tear secondary to AMD and may help to stabilize or even improve acuity in some cases^[10,20].

ACKNOWLEDGEMENTS

Foundations: Supported by the Natural Science Foundation of Zhejiang Province (No. LY16H120002); Zhejiang Province Medical Platform Program Grant (No. 2013RCB008).

Conflicts of Interest: Chen ZQ, None; Ye PP, None; Fang XY, None.

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