Tears of The Retinal Pigment Epithelium – A Review

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Abstract
Tears of the retinal pigment epithelium (RPE) may occur in eyes with a large pigment epithelial detachment (PED). They are most commonly associated with vascularized RPE detachment due to age-related macular degeneration (AMD) and usually involve a deleterious loss in visual acuity. With the extensive use of anti-vascular endothelial growth factor (anti-VEGF) therapy for treatment of eyes with neovascular AMD, recently there has been an increase in the incidence of RPE tear. Multimodal retinal imaging techniques help in accurate detection of RPE tears and help in identifying eyes with high risk factors for RPE tears formation. Understanding the pathogenesis and risk factors of RPE tears is important for better management of these eyes as RPE tears are associated with poor visual prognosis, especially if the fovea is involved. This review summarizes the current knowledge on RPE tear pathogenesis, risk factors for an impending tear, and approach to management of these eyes before and after RPE tear formation.

Keywords: retinal pigment epithelial tears, retinal pigment epithelium rip, neovascular age-related macular degeneration, pigment epithelial detachment, central serous chorioretinopathy, anti-vascular endothelial growth factor

Introduction
Tears of the retinal pigment epithelium (RPE) were first described by Hoskin et al in pigment epithelial detachments (PED) associated with neovascular age-related macular degeneration (AMD) as a rip in the detached RPE. Although RPE tears have also been described in association with several etiologies such as retinal angiomatous proliferation, polypoidal choroidal vasculopathy, central serous chorioretinopathy (CSC), angioid streaks, and trauma, they are most commonly associated with vascularized PEDs due to neovascular AMD.

Casswell et al reported a 10% spontaneous RPE tear rate of vascular PEDs in AMD. Previously known to occur spontaneously in the course of a PED, RPE tears may also occur after various treatments for neovascular AMD and CSC such as laser photocoagulation, photodynamic therapy (PDT) and anti-vascular endothelial growth factor (anti-VEGF) therapies. RPE tear after intravitreal bevacizumab injection for the treatment of an occult choroidal neovascularization (CNV) due to AMD was first reported in 2006. On an average, there is a 17% incidence of RPE tears after anti-VEGF therapy for PED secondary to neovascular AMD. The characteristics of RPE tears were first described on fundus fluorescein angiography (FFA) in 1981. The evolution of retinal imaging in the recent years has contributed to a better understanding of RPE tear development on autofluorescence (AF) imaging and optical coherence tomography (OCT).

Clinical Presentation
RPE Tears In Neovascular AMD – “RPE rips”
Classically, an RPE rip has been described to occur along the margin between detached and attached RPE. The detached RPE retracts in an accordion like fashion toward the opposite side of the PED, resulting in folds in the retracted RPE. As the torn edge of the RPE retracts, a well-demarcated area of underlying Bruch’s membrane and choroid becomes exposed.

On fundoscopy, an RPE tear appears as a crescentic well-demarcated area of bare choroid, parallel to the temporal edge of the PED, which has a bordering hyperpigmented area immediately adjacent to it. This hyperpigmented area represents the redundant, retracted RPE which is oriented parallel to the margin of the tear (Figures 1a, 2a, 3a). The overlying neurosensory retina remains intact and a localized neurosensory detachment may be present. RPE tears are often accompanied by hemorrhage or exudates. Bleeding is usually localized to the sub-retinal space but may break through into the vitreous when severe. After an RPE tear occurs, the torn edge of RPE reattaches to Bruch’s membrane at a new site and forms a smaller PED or results in flattening of the PED. Over time, the area of bare Bruch’s membrane may be replaced by normal-appearing RPE or become covered by fibrous tissue.

They result in sudden and severe loss of vision and have a poor visual prognosis even if the subfoveal area is spared. Rarely, eyes with tears not involving the fovea or through the fovea have been reported to retain good vision. Sarraf et al introduced an RPE tear grading system based on the longest linear diameter in the vector direction of the tear. Grade 1 tears were defined as <200μm. Grade 2 tears were between 200μm and 1 disk diameter. Grade 3 tears were >1 disk diameter. Grade 4 tears were subfoveal grade 3 tears. According to them, the lower grade tears have a better visual prognosis and better response to anti-VEGF therapy.

RPE Tears In Central Serous Chorioretinopathy – “Blow-outs of the RPE”
Goldstien and Pavan described two patients with defects in the RPE underlying a neurosensory elevation. Both their cases occurred in middle aged men in the setting of severe CSC. They postulated these cases to represent a...
distinct entity apart from RPE tears as previously described with vascularized PEDs. The RPE defects in these cases appeared at the dome of the PED in contrast to an RPE rip in neovascular AMD which occurs along the margin of a PED. Also, the edges of the defect were not retracted as is common in an RPE rip. (Figure 4)

They preferred the term “RPE blow-outs” for these RPE defects at the apex of a PED, where the intense leakage of fluid was suspected to lead to weakening and eventual disintegration of the overlying RPE cells. Subsequently, RPE tears including RPE rips have been reported in CSC which may occur spontaneously, after steroid use or after treatment.

**Imaging**

**Optical Coherence Tomography (OCT)**

OCT is useful in confirming the presence of an RPE tear. The RPE defects in these cases appeared at the dome of the PED in contrast to an RPE rip in neovascular AMD which occurs along the margin of a PED. Also, the edges of the defect were not retracted as is common in an RPE rip. (Figure 4)

They preferred the term “RPE blow-outs” for these RPE defects at the apex of a PED, where the intense leakage of fluid was suspected to lead to weakening and eventual disintegration of the overlying RPE cells. Subsequently, RPE tears including RPE rips have been reported in CSC which may occur spontaneously, after steroid use or after treatment.

**Fundus Autofluorescence (FAF)**

FAF imaging allows for an in-vivo, non-invasive evaluation of the RPE. In FAF imaging, areas of RPE tears exhibit a loss of AF signal as RPE cells responsible for autofluorescence are absent. Whereas, the adjacent area of retracted RPE exhibit an increased AF signal (Figure 1c,2c,3c). Small tears are more evident on FAF imaging and are easier to detect than on fundoscopy due to the high contrast of the hyperautofluorescent areas compared with the intact retina. Mendis and Lois observed “RPE resurfacing” of the area debrided of RPE over time on FAF imaging. It was evident as recovery of the AF signal, which occurred centripetally from the edge of the area of the RPE defect.

**Fundus Fluorescein Angiography (FFA)**

RPE tears have a distinctive appearance on FFA. The bare choroid appears as a sharply demarcated area of hyperfluorescent window defect which lies adjacent to an area of blocked hypofluorescence, corresponding to the layer. OCT also aids in differentiating RPE tears in AMD from geographic atrophy, especially if the tear is chronic, as it can detect the torn RPE layer. The PED height can be assessed on OCT for risk analysis for RPE tear occurrence in a large PED. Another parameter that can be assessed on OCT for risk analysis is the choroidal thickness (CT). Bhavsar et al measured the CT on spectral-domain OCT (SDOCT) in patients with RPE tear in one eye and found a significant decrease in subfoveal CT in eyes with RPE tear (154.9 ± 10.1 mm) compared with their normal fellow eye (212.9 ± 10.6 mm).
Alternating light and dark bands of the RPE may be appreciated by FFA and represent redundant, folded, or pleated RPE. Additional findings such as leakage within the bed of the RPE tear due to persistent CNVM and pooling of dye within the PED may also be seen. The size of the PED in diameter can be assessed on FFA as a high risk factor for RPE tear development. 

Mechanism of RPE Tears

The pathogenesis of RPE tear formation continues to remain controversial. The hypothesis by Gass in 1984 was based on a hemodynamic theory. According to his theory, RPE tears could occur because of rapid changes in vascular permeability of the neovascular membrane, which could induce sudden enlargement of the PED to a point where the RPE cells cannot withstand the pressure required to separate it from Bruch’s membrane, and a tear occurs at the junction of the attached and detached RPE. Krishan et al suggested the importance of mechanical factors in the development of RPE tears and proposed that a PED resembles the model of a deflected metal plate. According to this model, as the height of the PED increases, tangential stress at the base of the PED would increase at a substantially greater rate than the force at the center of the PED. Atrophic changes in the RPE also contribute to its weakening and make it vulnerable to mechanical stress, resulting in a tear at the base of the PED, which is the site of greatest bending stress. The angulation of the RPE at the base of the PED also weakens it, predisposing to rupture in this area. Increased fluid in the sub-pigment epithelial space leading to the development of a PED could be derived from the choroidal vasculature in the form of an occult CNV or a hyperpermeable choroid or from the RPE. The RPE normally pumps fluid from the neurosensory retina towards Bruch’s membrane because of active transport of ions. An increase in the resistance of the Bruch’s membrane to this fluid transport may lead to accumulation of fluid between the RPE and Bruch’s membrane. Age related changes in Bruch’s membrane with deposition of hydrophobic drusens reduces its permeability to water. As RPE tears have been reported to occur bilaterally, Chuang and Bird hypothesized that the age-related changes in Bruch’s membrane in eyes destined to manifest tears are different from those at risk of developing primary CNV. They found more confluent drusens with less fluorescence on FA in the fellow eyes of patients with RPE tears compared to fellow eyes of patients with primary neovascular lesions (Figure 5). The hypofluorescence of these drusens was due to their hydrophobicity, which limited entry of fluorescein into the lesions. According to them, presence of a CNV is not mandatory for the occurrence of an RPE tear and stressed on the importance of such hydrophobic deposits which increase the resistance of the Bruch’s membrane to water flow. Based on the observation of RPE tears occurring during or after photocoagulation, Gass described the role of tangential force on the RPE layer produced by a contracting CNV and proposed that the heat generated by photocoagulation caused a shearing force responsible for the tear. As significant changes in the hydrostatic pressure within the
PED are not expected acutely, the tractional forces induced by contraction of CNV may be the primary causative force for an RPE tear formation in such cases. Other treatment modalities, such as PDT\(^{52}\) and anti-VEGF therapy\(^{50}\) may also cause RPE tears by similar mechanism.

In the anti-VEGF era, with the increase in the reported incidence of RPE tears in AMD after therapy\(^{14,20,50-55}\), the focus has shifted in support of the original tractional CNV theory by Gass. There is also supportive histopathological evidence\(^{56,57}\) which found the under surface of the torn RPE to be adherent to a contiguous underlying plaque of CNV. After correlating their light microscopic findings with the FA characteristics of the RPE tears, Lafaut et al\(^{57}\) suggested the presence of neovascular tissue within the bed of the RPE tear, as well as the site of the retracted RPE. Spaide\(^{58}\) studied the internal structure of PEDs in AMD by enhanced depth imaging OCT and described reflective material suggestive of fibrovascular proliferation along the back surface of the RPE in PED and subsequent contracture of the material after intravitreal ranibizumab. They strongly proposed the neovascular origin of PEDs, but suggested that Bruch’s membrane also contributes to PED formation, as the exudation from the CNV may exceed the outflow ability of a relative hydrophobic Bruch’s membrane.\(^{46}\) However, in the setting of CSC where there is no neovascular membrane, occurrence of RPE tears can be explained by the hemodynamic theory. RPE detachments are commonly noted in CSC as choroidal hyperpermeability leads to serous PEDs.\(^{59}\) The detached RPE of a large PED is mechanically stressed and may develop RPE leaks due to decompensation, micro-rip of RPE or frank RPE tear.\(^{59,60,61}\)

RPE tear in CSC may occur spontaneously in a large serous PED\(^{59}\) or may be precipitated by an exacerbating factor such as steroid use which results in increased fluid accumulation within the PED due to increase in choroidal hyperpermeability\(^{33}\) or increase in fibrin exudation which may generate traction.\(^{62}\)

Goldstein and Pavan noted “blowouts of the RPE” at the dome of the PED without any retraction or rolling of the torn RPE layer.\(^{59}\) In one case the site which showed tremendous leakage of dye into the subretinal space on FFA, was later noted to develop a RPE defect. Hence, they suggested that the intense leakage across the RPE in CSC can lead to weakening and eventual disintegration of these cells, causing ‘RPE blow-out’. Later on, similar cases of apical RPE atrophy in PEDs have been described in CSC.\(^{63,32}\)

**Risk Factors For An Impending RPE Tear**

With better understanding of RPE tears over the last decade, several researchers have tried to identify risk factors to predict an RPE tear. A large PED marks the inference of an RPE tear. PED height is a reliable and measurable parameter to quantify a large PED on OCT (Figure 6). Chan et al\(^{64}\) reported an increased prevalence of RPE tears in PED lesions higher than 400µm, especially in the presence of increased subretinal fluid. Leitritz et al\(^{47}\) also described an increasing probability of RPE tears in PEDs greater than 400µm in height. Doguizi and Ozdek\(^{59}\) statistically determined 580µm as a cut-off point of PED height for the risk of an RPE tear. Similarly, a baseline height of 550 µm was described as a high-risk factor for the subsequent development of an RPE tear by Sarraf et al.\(^{32}\)

Chiang et al\(^{22}\) used both FA and OCT analysis to assess PED size. They found that large PED basal diameter on FFA and vertical height on OCT are correlated with an increased risk of developing an RPE tear after anti-VEGF therapy. In addition to basal linear diameter of PED, Chan et al\(^{55}\) also measured the surface area of the PED on FFA and reported large PED size as a predictor for RPE tears. They observed PED lesions with a smaller ratio of CNV size to PED size to have a stronger tendency for RPE tear. This could imply that a smaller CNV has more room for migration under a much larger PED, thus generating increased tangential stress on the RPE as contraction occurs in response to anti-VEGF therapy.

Duration of PED as a risk factor for RPE tears was reported by Doguizi and Ozdek,\(^{59}\) who found an inverse relationship between the duration of PED and RPE tear formation. They postulated that the neovascular process is fresh in a short duration of PED, with immature vessels. These immature vessels are more susceptible to anti-VEGFs and may have a more dramatic response to anti-VEGF therapy. As contractile forces generated by a CNV are believed to result in an RPE rip, clinicians consider any evidence of an underlying CNV, such as presence of heme, exudate, notched PED contour on OCT, hot spot or irregular fluorescence on angiography as high risk characteristics for such PEDs. Recently, detection of increased reflectance signals on confocal scanning laser ophthalmoscopy near-infrared images has been observed.
as a predictive marker for an impending RPE tear. These hyperreflective lines characteristically originate from the edge of PED lesions and correspond to the CNV localization observed on FFA, as well as with folds in the RPE seen on spectral domain OCT.\(^6,^9\)

Microrips of the RPE are also considered as a risk factor for RPE rips.\(^67\) Microrips are microscopic RPE defects detectable on OCT and represent grade 1 RPE tears of the classification system introduced by Sarraf et al.\(^27\) It is postulated that microrips probably lower the threshold of RPE resistance and make it vulnerable to the contraction forces generated after anti-VEGF therapy, hence resulting in anatomic failure of the RPE.

**Management**

Management of eyes with PEDs with high risk characteristics for an impending RPE tear is a challenging situation. An individualized approach is required after discussing the risk of an RPE tear formation after anti-VEGF therapy, as well as the possibility of progression of the disease activity without any treatment with the patient. A complete evaluation and documentation on FFA, OCT and FAF is important both pre and post-injection to guide the treatment approach. Anti-VEGF therapy may be discontinued temporarily, if signs of RPE tear formation appear or risk factors increase, and reconsidered when safe. There is no clinical data available currently, regarding the safety profile of the different anti-VEGF agents in these high-risk PED eyes; However, a higher incidence of RPE tears has been reported with higher dose of Ranibizumab (2mg vs 0.5mg).\(^68\)

As RPE tears may result in severe loss of vision, it is important to prognosticate these eyes, if an RPE tear develops. Smaller Grade 2 and Grade 3 tears may demonstrate visual improvement with continued anti-VEGF therapy.\(^27\) However, Grade 4 tears have poor visual prognosis and are not associated with improved visual acuity after sustained anti-VEGF therapy, although continued treatment may help to maintain visual acuity and prevent further deterioration.\(^52\)

There are several reports of functional and anatomical improvement after anti-VEGF therapy, for spontaneous RPE tears and RPE tears after therapy.\(^50,^27,^69,^72\) Based on the currently available data, continuing anti-VEGF treatment after RPE tear development based on the presence of disease activity, is recommended. However, this should be done under constant re-evaluation, due to risk of progression of RPE tears with therapy. The fellow eyes of patients with RPE tears in one eye also warrant close observation.\(^47,^48\)

**Conclusion**

Previously an enigma, today clinicians have a better understanding of RPE tear formation and high-risk PEDs, due to availability of supportive data. With the evolution of multimodal retinal imaging techniques, and growing popularity of anti-VEGF therapy in AMD, the incidence of RPE tear formation has increased. It is important for ophthalmologists to be able to identify the high-risk PEDs before starting therapy, and formulate the safest possible treatment plan for each patient. However, further studies are needed to compare the available anti-VEGF agents, with respect to their role in development of RPE tears, and efficacy as treatment for high risk PEDs and RPE tears, to study the role of PDT in treatment of RPE tears, and application of OCT angiography in the management of high risk PEDs and RPE tears.

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