Retinal Pigment Epithelial Tears (Rips) in the ERA of Anti Vegf - When and Why?

Aim of Study
Tears of the retinal pigment epithelium (RPE) are a recognized complication that occur in patients with retinal pigment epithelial detachment (PED) associated with neovascular age-related macular degeneration (wet AMD) and related conditions such as polypoidal choroidal vasculopathy (PCV) and retinal angiomatous proliferation (RAP). While rips following PDT has been reported in literature, rips following anti VEGF therapy, though reported, have not been studied in detail. As anti VEGF therapy is the mainstay in the treatment of wet AMD including PCV, the study of RPE rips is more relevant in the present scenario. This retrospective study is aimed at evaluating the clinical profile, etiopathogenesis, morphological characteristics, evolution and prognosis of RPE tears in eyes with AMD treated with anti VEGF therapy.

Materials and Methods
This was a retrospective analysis of 95 eyes with retinal pigment epithelial detachments due to various etiologies that presented between January 2012 and January 2013 which received anti VEGF therapy with a minimum follow up of 6 months. PEDs were characterized based on spectral domain OCT and angiographic findings. Prior treatments, nature of the lesion, time to tear, and pre-injection and final visual acuities were all studied. Eyes with rip were compared to those without and an evaluation of predictive factors was done. Management and outcome of these eyes were also analyzed.

Results
Among 95 eyes studied, 11 cases (11.58 %) of RPE rips were noted during follow up. RPE rips were more common in PEDs with internal reflectivity (82 %) than in PED’S without (18 %). Rips following anti VEGF were more likely to occur with PEDs >1000μm diameter and > 400μm height compared to eyes with no rip which had smaller PEDs. Rips frequently occur at the fovea (71.43 %) than elsewhere. All these eyes continued to receive anti VEGF therapy and showed an improvement in visual acuity from baseline. The mean post-treatment visual acuity was 6/36, compared to the pre-treatment vision of 1/60.

Conclusion
Retinal pigment epithelial tears are infrequent complications in eyes with PED undergoing anti VEGF treatment. Eyes with large and tense vascular PEDs are at greatest risk. In spite of the predilection for the fovea, continued treatment with Anti VEGF resulted in improved visual outcome.

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OCT, digital fundus fluorescein angiography (FFA) and Indocyanine Green angiography (ICGA) of HRA Spectralis to confirm the presence of PED and neovascularization (Fig 1). Prior treatments, nature of the lesion, time to tear, and pre-injection and final visual acuities (Snellen and logMAR) were all studied. PEDs were characterized based on their internal reflectivity (serous, fibrovascular, haemorrhagic and drusenoid), largest basal diameter (μm) and maximum height (μm). Eyes with RIP were compared to those without and an evaluation of predictive factors was done. Management and outcome of these eyes were also analyzed.

Treatment of the PED was recommended in the presence of sub-retinal or intra-retinal fluid and deterioration of best-corrected visual acuity (BCVA). Intravitreal anti-VEGF therapy was given in accordance with PRONTO schedule with either 0.5mg/0.05ml ranibizumab or 1.25mg/0.05ml bevacizumab. The initial treatment consisted of 3 monthly injections in all patients. The patients were followed up 2 weeks after each injection. After completion of 3 injections, follow-up examinations were scheduled at 6 weekly intervals, or less frequently if no new visual symptoms developed or visual acuity remained stable. The BCVA, fundus evaluation by slitlamp biomicroscopy, FFA/ICG angiography, and OCT were done to assess the morphological and functional changes after treatment. Retreatment was recommended if there was decrease in visual acuity in association with new or increased sub-retinal or intra-retinal fluid. Presence of PED alone was not an indication for retreatment. Patients who responded poorly to anti VEGF therapy received combination therapy with PDT. None of the patients developed any intra operative complications or post operative adverse drug events.

The difference in morphological features of PEDs such as internal reflectivity, largest basal diameter and maximum height in eyes with and without rips were compared. The time at which the RPE tear developed following anti-VEGF therapy and influence on final visual outcome were analyzed. Adjacent RPE abnormalities (thinning, irregularity, and absence), inner segment-outer segment (IS-OS) loss and scarring were also noted.

Statistical Methods: Independent t-test was used for assessing the statistical significance between the groups of non-rip eyes and rip eyes for their PED diameter and height. Paired t-test was used to assess the statistical significance of pre-rip and post rip final visual acuity among the 11 rip eyes.

Results
Among 95 eyes studied, 11 cases (11.58%) of retinal pigment epithelial tears (RPE rips) were noted during follow up. Of these, 7 eyes (63.63%) were due to PCV and 4 eyes (36.36%) were due to typical late AMD. The development of RPE tear following anti-VEGF therapy were observed within 8 days to 12 weeks after the intra vitreal injection (mean 26.82 days SD± 25.51 days). In our case series, 7/11 eyes (63.63%) developed rip within 2 weeks of the very first injection of Bevacizumab. We could pick up this abruptness of RPE rip due to our scheduled first follow up at 2 weeks after every injection. The mean number of injections received before the occurrence of RIP was 1.45. The median time interval between the injection and RIP was 2 weeks.

Figure 1: Case No: 8; Clinical photographs initially after RIP (1a), after reasonable resolution (1b) and ICG angiography (1c)

Figure 2: Time to rip in days among eyes with rip
RPE rips were more common in PED’s with internal reflectivity (9/11, 82%) than in PED’s without (2/11, 18%). Among the RIP eyes, there were 7 fibrovascular, 2 hemorrhagic and 2 serous PEDs. Sub-retinal fluid was present in all 11 cases and intra-retinal fluid in 3 eyes. The rip was located at the base of the PED in all cases. The average basal diameter of PED in non-rip eyes was 1636.29 μm (±SD 908.10 μm) and in rip eyes was 3547.63 μm (±SD 1047.2 μm). The difference in average basal diameter between the two groups was highly significant (p=0.0001). Average height of PED in non-rip eyes was 238.6 μm (±SD 108.12 μm) and in rip eyes was 629.55 μm (±SD 92.65 μm). (Fig 4). The difference in the average height between the two groups was also found to be highly significant (p=0.0001). All the RIP eyes had PEDs >1000 μm in diameter and > 400 μm in height whereas most of the eyes without rip had smaller PED’s. 2 patients (2/11, 18%) who had a spontaneous rip in one eye developed rip in the fellow eye following anti VEGF. 1 patient who underwent combination therapy developed RIP after PDT. All RIP eyes continued to receive anti VEGF therapy as scheduled. 1 eye which had un-resolving vitreous hemorrhage underwent vitrectomy and 1 eye received pneumatic displacement along with anti VEGF therapy.

Vision improved in 9/11 eyes (82 %), stabilized in 1 eye (9.09 % ) and decreased in 1 eye (9.09 % ). Among the RIPs, 8 (72.72 %) were foveal rips and 3(27.27 %) were extrafoveal. The mean final visual acuity among the foveal rips was 6/60 and among the extra foveal rips was 6/12. Even though there was a drop in vision noticed at the time of RPE tear in those cases of foveal rips, the final visual acuity was still better than pre-treatment vision. The mean post-treatment visual acuity was 6/36, which showed a significant improvement from the mean pre-treatment vision of 1/60 (p=0.005). The final visual acuity also improved in both the cases where vitrectomy and pneumatic displacement was done, with the former having extra foveal rip and the latter a foveal rip. None of the patients developed any intra operative complications or other post operative ocular complications or systemic side effects infrequently reported with anti VEGF therapy.

Figure 3: OCT images of Case No: 8 prior to rip (1a), after occurrence of rip (2a) and following resolution and scarring (3a)

Figure 4: Distribution of PED diameter(μm) and height(μm) among Rip and Non-rip eyes
Discussion

Retinal pigment epithelial tears are documented as a complication that can occur in the natural history of evolution of neovascular age-related macular degeneration with associated retinal pigment epithelial detachment\(^1\) or following treatment with laser, photodynamic therapy (PDT) or intravitreal anti vascular endothelial growth factor (anti VEGF) treatment.\(^2\) Incidence of RPE tear in eyes with exudative AMD is reported between 2% to 6% where as it is 12% to 25% in those with a preexisting PED.\(^3\) The generally poor visual outcome in RPE tears occurring spontaneously or following laser photocoagulation or photodynamic therapy (PDT) were attributed to massive subretinal bleeding, disciform scarring or atrophy in the RPE-free area, and development of rip was considered an end stage phenomenon where no treatment was possible.\(^4\) But with the advent of Anti VEGF, the scenario has changed for the better. Inspite of the occurrence of rip, consolidation of the neovascular process and significant improvement in visual acuity from baseline were observed in majority of these eyes.

The incidence of RPE tears during anti-VEGF therapy in eyes with PED has been reported in about 12–17% of treated eyes.\(^5,6,7,8\) Similar to that reported for the natural history of untreated PED,\(^1\) In our study rips occurred in 11.58%. The relatively quick occurrence of RPE tears within 2 weeks of initiation of anti VEGF therapy needs speculation. The mechanisms postulated are the rapid reduction in fluid with collapse of huge PED in response to anti AEGF therapy, mechanical contraction of tissue due to shrinkage of CNVM or from a loss of RPE integrity.\(^5\) The most commonly reported tractional event following anti VEGF therapy is RPE tear.\(^9\) It has been reported that the rate of rip following anti-VEGF therapy was higher than that observed in elderly patients not receiving therapy (10%).\(^10\) In a multicenter study of 1,280 eyes receiving intravitreal bevacizumab, 16.8% of eyes with vascularized PEDs developed RPE tear with vertical height being the only significant risk factor in a multivariate analysis.\(^6\) In another study involving 60 eyes, no difference were noticed between the agents used (Ranibizumab, Bevacizumab and Pegaptanib), with the basal diameter and vertical height significantly increasing the risk.\(^7\) Chan et al have suggested that the exclusion of patients with preexisting RPE detachments in the pivotal pegaptanib and ranibizumab trials may explain the very low occurrence of RPE tears in these trials.\(^8\) Our study also brings out the fact that rips were more common in PED eyes. As discussed by various authors, we also found >1000 μm diameter and >400 μm height of the PED as a significant risk factor for RIP in these eyes. Chan et al have also reported a PED height of >400 μm as a significant risk factor for RPE tears.\(^9\)

The visual outcome in rip eyes was generally good in our study. Improvement in vision occurred in 82% of eyes. Foveal location of rip was common (72.72%) and a major limiting factor for the poorer visual prognosis in this group.\(^11\) Varying frequency of foveal involvement from 23% to 75% has been quoted in literature.\(^5,11,12\) This highlights the unpredictability of the location of rips which will ultimately depend on the initial location of the PED and the subsequent direction of tractional vectors in relation to the fovea. A gradual decrease in vision with increasing RPE contraction has also been reported.\(^13\) A major limitation of our study is the relatively small sample size and further prospective studies in larger series with longer duration of follow up is recommended to arrive at a definitive conclusion regarding the outcome of retinal pigment epithelial tears in eyes with PED undergoing anti VEGF treatment.

Conclusion

Retinal pigment epithelial tears are infrequent complications in eyes with PED undergoing treatment with anti VEGF agents and occur usually 2 weeks after intravitreal injection. The dimensions and content of the PEDs are helpful in predicting this risk and eyes with large and tense PEDs and those with internal reflectivity (vascularity) are at greatest risk. The relatively rapid onset of this complication with therapy, the need for continuation of therapy despite the occurrence of rip and the possible adverse effects on long term visual outcome must be taken into consideration in eyes at risk and explained to the patient beforehand. If one eye had already developed a spontaneous rip, then the risk of developing rip in the fellow eye is increased with therapy. In spite of the predilection for the fovea, continued treatment with Anti VEGF resulted in improvement or stabilization of vision.

References
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