Clinicopathological correlation of retinal pigment epithelial tears in exudative age related macular degeneration: pretear, tear, and scarred tear

B A Lafaut, S Aisenbrey, C Vanden Broecke, R Krott, C P Jonescu-Cuppers, S Reyniers, K U Bartz-Schmidt

Abstract

Aims—To analyse the histopathology of vascularised pigment epithelial detachments and tears of the retinal pigment epithelium (RPE) in age related macular degeneration (AMD).

Methods—The light microscopic architecture of 10 surgically removed subretinal specimens—three vascularised pigment epithelial detachments, four recent tears, and three scarred tears as a manifestation of AMD—were studied and correlated with the angiographic findings.

Results—Recent tears: a large fibrovascular membrane was found to be originally situated in Bruch’s membrane. About half of the surface of the fibrovascular tissue was denuded of RPE and diffuse drusen. The RPE and diffuse drusen had retracted and rolled up, covering a neighbouring part of the intra-Bruch’s fibrovascular membrane. The rolled up RPE and diffuse drusen were not interspersed with fibrovascular tissue but lay superficial to the intra-Bruch’s fibrovascular membrane itself. Scarred tears: a collagen capsule surrounded the rolled up diffuse drusen and RPE. Fibrovascular tissue was found inside the rolled up material, predominantly at its choroidal side.

Conclusion—The area of choroidal neovascularisation associated with a vascularised pigment epithelial detachment and a tear of the RPE may be larger than was hitherto thought or indicated by fluorescein angiography. This neovascular tissue may be present within the bed of the RPE tear, as well as at the site of the rolled up RPE.

(Clinical examination of 10 surgically removed submacular tissue in three eyes with a vascularised PED and in seven eyes with a tear of the RPE. We suggest a flow chart of events that eventually lead to a scarred tear supported by the available clinicopathological studies. This may contribute to a better understanding of this vision threatening complication of age related macular degeneration.

Materials and methods

STUDY POPULATION

All surgical specimens from eyes with either a PED or a spontaneous tear of the RPE selected from a consecutive series of 200 age related macular degeneration specimens are included in this study with the exclusion of eight PED associated with a “deep retinal vascular anomalous complex” or a “chorioretinal anastomosis” which are the subject of a separate study. Three eyes with a vascularised PED (cases 1–3) as well as seven eyes with an established tear (cases 4–10) were included. All patients had experienced a recent tear in visual acuity (within 3 months) in the study eye except for three patients with a less recent tear of the RPE (cases 8–10).

CLINICAL EXAMINATION

All 10 patients had a standard ophthalmological examination including fundus photography and fluorescein angiography not more than 14
Table 1  Summary of the clinical findings

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Tearing</th>
<th>Fundus and fluorescein angiographic findings</th>
<th>Indocyanine green angiographic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>61</td>
<td>—</td>
<td>Vascularised PED, non-homogeneous filling</td>
<td>Underlying ill defined plaque</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>79</td>
<td>1 month</td>
<td>No subretinal fibrosis, some surrounding blood vascular net at level of rolled up RPE, marginal hot spot on indocyanine green angiography</td>
<td>Plaque occupying entire lesion/PED</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>63</td>
<td>—</td>
<td>Vascularised PED, notch</td>
<td>Marginal hot spot</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>78</td>
<td>1 month</td>
<td>Tearing vascularised PED, vascular net inside PED small subretinal haemorrhages at one edge</td>
<td>Speckled hyperfluorescence in rolled up RPE, surrounded by plaque, denuded area isofluorescent</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>75</td>
<td>4–6 weeks</td>
<td>No subretinal fibrous tissue, no vascular net</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>80</td>
<td>2 months</td>
<td>Vascular net at level of rolled up RPE and in the area of denuded RPE</td>
<td>Speckled hyperfluorescence in rolled up RPE disappearing within a hyperfluorescent plaque, denuded area included Marginal plaque</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>75</td>
<td>2 ½ months</td>
<td>Rolled up RPE embedded in massive subretinal haemorrhage, no vascular net</td>
<td>Speckled hyperfluorescence in rolled up RPE</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>65</td>
<td>4 months</td>
<td>Some subretinal fibrosis, some surrounding blood no vascular net</td>
<td>Speckled hyperfluorescence in rolled up RPE, surrounded by plaque, denuded area hyperfluorescent</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>76</td>
<td>3 months</td>
<td>Vascularised PED, notch</td>
<td>Speckled hyperfluorescence in rolled up RPE</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>75</td>
<td>5–6 months</td>
<td>Rolled up RPE surrounded by subretinal fibrous tissue and massive subretinal haemorrhage</td>
<td>Speckled hyperfluorescence in rolled up RPE</td>
</tr>
</tbody>
</table>

Previous angiographic documentation, indicated in italics, is available for four patients. The indication of time corresponds to the time interval between first and second angiographic examination.

Results

The fluorescein and indocyanine green angio-graphic findings of these patients are summarised in Table 1.

PRETREAT STAGE—PED

Two of three PED had pretreat characteristics (cases 1 and 2)—namely, a non-homogeneous filling with a paracentral hypofluorescent zone. Indocyanine green angiography revealed a plaque underlining the PED in these two cases. Fibrovascular tissue was found in the two corresponding specimens. In one specimen the fibrovascular membrane was located with certainty in the Bruch’s membrane or under the RPE as it was entirely covered by RPE and diffuse drusen; however, in the central two thirds of the specimen the RPE and diffuse drusen had detached from the fibrovascular membrane itself (Fig 1). The fibrovascular membrane of the other specimen could not be oriented as no adherent RPE and diffuse drusen were found on serially sectioned material, but RPE and diffuse drusen were located distant from the fibrovascular membrane itself. The third PED (case 3) had a notch on fluorescein angiography that corresponded to a marginal hot spot on indocyanine green angiography. Fibrovascular tissue was found that was at least in part located in the Bruch’s membrane. Another part of the membrane could not be oriented as it was not covered by RPE and diffuse drusen. Some RPE and diffuse drusen were located distant from the fibrovascular tissue.

FRESH TEAR STAGE

Three relatively recent tears of the RPE with characteristic angiographic features (cases 4, 5, and 7) had a rather similar histoarchitecture. A large fibrovascular membrane was found to be originally situated in the Bruch’s membrane since at its edges native RPE and diffuse drusen were recognised and allowed orientation (Figs 2 and 3). About half of the surface of the fibrovascular tissue was denuded of RPE and diffuse drusen except for its outer margin.
The RPE and diffuse drusen appeared to have retracted and rolled up, covering a neighbouring part of the intra-Bruch’s fibrovascular membrane. The rolled up RPE and diffuse drusen were not interspersed with fibrovascular tissue but lay superficial to the intra-Bruch’s fibrovascular membrane itself. The rolled up RPE and diffuse drusen were partially covered with non-homogeneous fluorescein filling. Indocyanine green angiography revealed an ill defined underlying plaque (case 1). The RPE and diffuse drusen have partially detached from the intra-Bruch’s fibrovascular tissue. Masson trichrome, bar = 100 µm.

Figure 1 Specimen corresponding to a vascularised pigment epithelial detachment with non-homogeneous fluorescein filling. Indocyanine green angiography revealed an ill defined underlying plaque (case 1). The RPE and diffuse drusen have partially detached from the intra-Bruch’s fibrovascular tissue. Masson trichrome, bar = 100 µm.

Figure 2 Specimen corresponding to a recent tear (case 5). (A) At one edge of the specimen intra-Bruch’s fibrovascular tissue is recognised, more centrally to it rolled up RPE and diffuse drusen are seen that are only partially covered by fibrovascular tissue and amorphous debris on their retinal side. (B) Towards the opposite edge, rather fibrous fibrovascular membrane is observed denuded of RPE and diffuse drusen but covered by a thin layer of amorphous debris. Periodic acid Schiff, bar = 50 µm in (A) and 25 µm in (B).
by proteinaceous debris and the remains of outer segments in two specimens partially covered by a thin fibrovascular membrane in one specimen and entirely covered by a thin fibrovascular membrane in another specimen. The covering fibrovascular tissue was only poorly vascularised. A moderately dense infiltration of inflammatory cells (predominantly lymphocytes) was seen in the neighbourhood of the rolled up RPE and diffuse drusen.

The angiographic appearance of case 6 was somewhat unusual: fluorescein angiography identified a vascular net with profuse leakage, indocyanine green angiography indicated the rolled up RPE with speckled hyperfluorescence embedded in a plaque. The corresponding specimen consisted of fibrovascular tissue located subretinally as well as under the RPE. The subretinal component was smaller in diameter than the intra-Bruch's component.
Rolled up RPE and diffuse drusen were identified in between the two components and a part of the sub-RPE component was denuded of RPE and BLD.

SCARRED TEAR STAGE (CASES 8–10)

Basically an identical architecture was recognised as well in the three scarred tears of the RPE. The presence of a collagen capsule surrounding the rolled up diffuse drusen or the rolled up diffuse drusen and RPE were the most marked characteristic: the capsule was thin in case 8 (Fig 4) but thick and dense in the other two (Fig 5). Fibrovascular tissue was found inside the rolled up material in cases 9 and 10, predominantly at its choroidal side. A moderate inflammatory cell infiltration was seen near the diffuse drusen in cases 8 and 10. Melanin bearing cells had migrated distant from the diffuse drusen, either towards the retinal surface of the capsule or towards the adjacent fibrovascular membrane denuded of RPE and diffuse drusen in cases 9 and 10. Such pigmented cells appeared to separate the densely collagenised capsule from the remainder of the specimen.

Discussion

It has recently been recognised that differing histoarchitectural characteristics may explain fluorescein angiographic features of age related choroidal neovascularisation. This study was undertaken to find out whether the architecture of a pretear PED and of a tear of the RPE could be reconstructed from a series of surgically removed specimens. We have used light microscopy as the major cellular components (RPE, vascular endothelium, fibrocytes, macrophages, and photoreceptors) as well as extracellular components (collagen, diffuse drusen, and fibrin) can be correctly identified by light microscopy alone. The diffuse drusen are seen as an extra layer between the RPE and the outer Bruch’s membrane (defined here as Bruch’s membrane), which is a granular, PAS positive deposition that stains metachromatically blue-purple on MTC. Diffuse drusen is a light microscopic term that corresponds to basal laminar and basal linear deposits, which are the electron microscopic characteristics of age related macular degeneration.

Because there are almost no clinicopathological correlations of neovascularised PED, the histoarchitecture of this lesion is only poorly known. Fluorescein angiography already gives an indication of the presence of neovascularisation when a notched or a reniform PED is demonstrated. Fluorescein angiography allows the identification of a “chorioretinal anastomosis” or a “deep retinal vascular anomalous complex” which is a peculiar lesion associated with a PED. The latter lesion is not further elaborated here. Specific types of vascularised PED have been described.
Finally, (E) represents a scarred tear. To fresh tears respectively without or with denuded intra-Bruch’s fibrovascular tissue, and PED with a plaque or hot spot, (B) corresponds to a pretear PED, (C) and (D) correspond lead to a scarred tear of the retinal pigment epithelium. (A) Corresponds to a vascularised PED in age related macular degeneration. It appears that in these two cases detachment of the RPE and diffuse drusen from the underlying fibrovascular tissue corresponds to the clinical PED. Another argument that RPE and diffuse drusen may detach from underlying fibrovascular tissue if present is that a tear corresponds to rolled up RPE and diffuse drusen without associated fibrovascular tissue in relatively fresh specimens (Fig 6D). Fibrovascular tissue grown into the rolled up RPE and diffuse drusen is, however, observed in more chronic, scarred lesions (Fig 6E). Furthermore, the overlying proteinaceous fluid may intuitively explain the poor angiographic indication of the associated choroidal neovascularisation. Intra-Bruch’s fibrovascular tissue was also found in the vascularised PED with a marginal hot spot. Unfortunately, the surgical specimens are fragile and may have been distorted when passing through the sclerotomy. More correlations will be needed to better understand the architecture of a vascularised PED.

Coscas et al and Gass indicated the role of associated occult choroidal neovascularisation in the process of tearing. Their concept has been reinforced since the advent of indocyanine green angiography. The rolled up RPE is hypofluorescent on fluorescein angiography due to blockage by its pigmentation. A characteristic speckled hyperfluorescence of a variable degree is observed on indocyanine green angiography that indicates the presence of underlying choroidal neovascularisation. The indocyanine green angiographic characteristics of tears are, however, more complex. The speckled hyperfluorescence of the rolled up RPE may be associated with a plaque that may partly or entirely occupy the area denuded of RPE. This angiographic finding suggests that choroidal neovascularisation may even be present in areas denuded of RPE. It is well known that tearing triggers the formation of a disciform scar and that a disciform scar may explain the presence of a plaque. However, such associated plaques are also found shortly after tearing of the retinal pigment epithelium before the tranformation into a scar has occurred. For example, we found a relatively large area of fibrovascular tissue, denuded of RPE and diffuse drusen neighbouring the rolled up tear in three of four relatively fresh tears (Fig 6D). This fibrovascular tissue may be responsible for the plaque surrounding the tear as was shown by indocyanine green angiography in the two examined cases. The observation suggests that choroidal neovascularisation is instrumental in the pathogenesis of pigment epithelial tears, but also indicates that the area of fibrovascular tissue may be more extensive than was hitherto thought. It is likely that the neovascular tissue had partly or entirely undermined the PED before tearing took place. This extent may not be readily recognised angiographically because of interference with the proteinaceous exudate of the overlying PED itself.

In conclusion, we suggest that the RPE with its diffuse drusen may progressively detach with indocyanine green angiography. Either a marginal hot spot (a late hyperfluorescence smaller than one disc area) or a marginal plaque (a late hyperfluorescence equal or larger than one disc area) are the typical lesions observed. The majority of these late hyperfluorescent lesions lie outside the PED itself. The hot spot or the plaque often correspond to a notch that was already identified by fluorescein angiography. It is hypothesised that these lesions correspond to intra-Bruch’s fibrovascular choroidal neovascularisation at the edge of a PED (Fig 6A). Less frequently, indocyanine green angiography may, however, reveal a plaque that has largely or even entirely undermined the associated PED as in cases 1 and 2. This angiographic pattern suggests the presence of an intra-Bruch’s fibrovascular membrane at the site of the PED (Fig 6B). The intra-Bruch’s fibrovascular tissue was demonstrated in at least one pretear specimen. An extensive area of separation of the RPE together with the diffuse drusen from underlying intra-Bruch’s fibrovascular tissue was observed. The detachment appears not to be an artefact because some proteinaceous fluid filled the lumen of the separation. In the second pretear specimen the RPE and diffuse drusen had entirely separated from the fibrovascular tissue. This would not have been likely if a pre-existing weakened adhesion was not present because it was not observed in a consecutive series of 31 classic or occult neovascular membranes without an associated clinicopathological correlation of retinal pigment epithelial tears in exudative AMD.
from the underlying intra-Bruch's fibrovascular membrane as a variant pathogenetic mechanism of a vascularised PED. It may not only explain a plaque largely undermining a PED but also a plaque surrounding torn RPE. Within a matter of months, the torn and rolled up RPE becomes embedded in a thick collagenous capsule, and melanin bearing cells, either RPE or melanophages, migrate. Both these changes may explain why the characteristic appearance of a tear of the RPE disappears with time.


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