

# MAJOR REVIEW

## Retinal Pigment Epithelial Detachment

Shiri Zayit-Soudry, MD,<sup>1,3</sup> Iris Moroz, MD,<sup>2,3</sup> and Anat Loewenstein, MD<sup>1,3</sup>

<sup>1</sup>Department of Ophthalmology, Tel-Aviv Sourasky Medical Center; <sup>2</sup>Retinal Imaging and OCT Unit, Goldschleger Eye Institute, Sheba Medical Center; and <sup>3</sup>Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

**Abstract.** Detachment of the retinal pigment epithelium is a prominent feature of many chorio-retinal disease processes, the most prevalent of which is age-related macular degeneration (AMD). Detachment of the retinal pigment epithelium may or may not be associated with choroidal neovascularization and may be caused by different types of pathogenesis, each associated with distinct angiographic features, natural course, visual prognosis, and response to treatment. The phrase “detachment of the retinal pigment epithelium” is used quite often, not always in the correct association and with no clear differentiation between its various types. It is important to identify the specific nature of detachment of the retinal pigment epithelium, and to establish an accurate diagnosis and treatment plan. Therefore, we present a review of the existing types of detachment of the retinal pigment epithelium with what we propose as being appropriate nomenclature and classification, and potential treatment recommendations. (*Surv Ophthalmol* 52:227–243, 2007. © 2007 Elsevier Inc. All rights reserved.)

**Key words.** age-related macular degeneration • choroidal neovascularization • occult CNV • retinal pigment epithelial detachment

### I. Introduction

Retinal pigment epithelium detachment (PED) is a prominent feature of many chorio-retinal disease processes, the most prevalent of which is age-related macular degeneration (AMD). Accurate interpretation of the clinical and angiographic findings in PEDs could be difficult, perhaps even to experienced retina specialists. The development of choroidal neovascularization (CNV) has been associated with long-standing PED, and as it poses an increased risk of severe visual loss, recognition of its presence and extent is a major concern. Because there are, as yet, no established recommendations for the treatment of PED, whether or not associated with CNV, the positive finding of PED may affect treatment management and thus may have long-term prognostic significance.

Several forms of PED have been reported. This review characterizes the pathogenesis, clinical features, angiographic appearance, natural course, and prognosis of various types of PED in AMD.

### II. Pathogenesis

The retinal pigment epithelium (RPE) monolayer, extending from the optic disk margin continuously into the ciliary body epithelium, is bounded on its apical surface by the apical surface of the retina and on its basal surface by the collagenous layer of Bruch's membrane (Fig. 1). Proper anatomical apposition between the retina, the RPE, and Bruch's membrane is crucial for nutritional support of the photoreceptors, retinol metabolism, phagocytosis of the photoreceptors outer segments, and

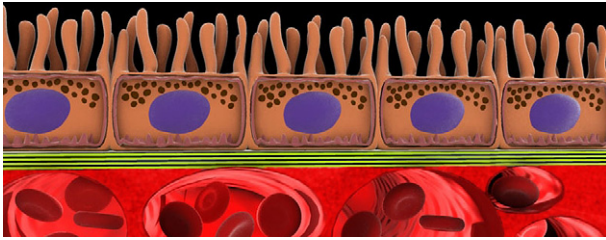


Fig. 1. Graphic illustration of the normal apposition between inner Bruch's membrane, the inner layer of which is formed by the basement membrane of the RPE cells, and the overlying retinal photoreceptors.

formation of the outer blood–retinal barrier, and thus for good visual function.<sup>2,105,115</sup> Microvilli present at the inner surface of RPE cells create interdigitations with the outer segments of the photoreceptors of the retina, enhancing their apposition. Inter-photoreceptor matrix further stabilizes the adhesion between the retina and the RPE.<sup>105</sup>

The forces maintaining normal adhesion between the RPE and Bruch's membrane are less well understood. Under normal conditions, there is a net bulk flow of fluid from the vitreous toward the choroid, with its generation depending on hydrostatic and osmotic forces within the two bodies. Both the RPE and the retina offer resistance to the fluid flow, but as the former has greater resistance due to its limited hydraulic conductivity, a vector force is generated pushing it against Bruch's membrane.<sup>69</sup> The attachment of the RPE basement membrane to Bruch's membrane is possibly complemented through regions of hemidesmosomes containing fine filaments of laminin, proteoglycans and collagen types IV and V.<sup>79</sup>

Detachment of the RPE occurs between the basal lamina of the RPE cell and the inner collagenous Bruch's membrane.<sup>86,121</sup> The etiology of PED can be divided into four major categories: inflammatory, ischemic, idiopathic, and degenerative. Inflammatory PED occurs when choroidal inflammation causes increased vascular permeability and breakdown of the outer blood ocular barrier,<sup>50</sup> with subsequent accumulation of fluid rich in protein under the RPE, as in Vogt-Koyanagi-Harada syndrome. In several pathologic states, such as malignant hypertension and eclampsia, ischemia of the retinal and choroidal vessel walls resulting from endovascular damage was suggested as a possible cause of breakdown of the blood ocular barrier leading to leakage and accumulation of fluid under both layers,<sup>117</sup> and formation of ischemic PED. The prototype of idiopathic PED is probably central serous chorio-retinopathy, in which choroidal

dysfunction resulting in multifocal hyperpermeability<sup>27,116</sup> combined with a defect in the RPE barrier allows abnormal leakage of fluid and protein into the sub-RPE and subretinal space.<sup>27,117</sup>

This review focuses on degenerative PED, which is the type associated with AMD.

#### A. PATHOPHYSIOLOGY OF DEGENERATIVE PED

Although PED can occur under diverse conditions in association with AMD, the precise differences between the pathogenic aspects of the various clinical entities, which will be specified subsequently, are not completely understood. The pathogenesis of PED in AMD is probably a continuum with that of degenerative changes occurring with age in Bruch's membrane, and formation of CNV. Generally, hydrophobic barrier formation in Bruch's membrane, as a result of several ultrastructural changes occurring with age, is commonly believed to be of paramount pathogenic significance.<sup>11,12,36,53,63</sup> Green et al have shown a direct relationship between aging and thickness of Bruch's membrane,<sup>54</sup> established both by light and electron microscopy. The generalized thickening was shown to be secondary to accumulation of waste products and deposition of lipids, as well as an increase in collagen content.<sup>10,79,98</sup> Pauleikhoff et al performed a histochemical and morphologic study of aging changes in Bruch's membrane.<sup>91</sup> A progressive accumulation of neutral lipids, possibly derived from degradation products of photoreceptor outer segments with relation to age, was associated with destruction of the native architecture of the tissue and implicated as a cause of photoreceptor dysfunction and PED occurring in AMD. Other works have also shown increased lipid content of Bruch's membrane, resulting from transport of partially digested phagocytized material from the RPE cells<sup>64,117</sup> to be associated with reduced hydraulic conductivity after 50 years of age.<sup>64,84,117</sup> These mechanisms occur more notably in the posterior pole.

Development of drusen, representing histologically localized accumulations of basal linear deposits,<sup>52,101</sup> is considered another manifestation of the diffuse pathology and formation of layer of debris just described. Drusen are seen clinically at the posterior pole of patients in their 7<sup>th</sup> decade, as pale yellow-white, typically 63–175  $\mu\text{m}$ , and are among the recognized ocular risk factors for development of CNV in patients with advanced AMD. Occasionally, the increased hydrophobicity and reduced hydraulic conductivity to fluid outflow from the vitreous toward the choroid prompts accumulation of fluid beneath the RPE, in spite of

continued pumping of the RPE,<sup>12,107</sup> and probably relate to pathogenesis of serous PED.

Another feature of AMD is PED associated with CNV, the precise pathogenesis of which is a matter of ongoing controversy. One theory, proposed by Gass in 1984, relates to ingrowth of new leaking vessels into Bruch's membrane and the sub-RPE space,<sup>40</sup> sometimes undetectably clinically, giving rise to elevated hydrostatic pressure within it and causing subsequent serous or hemorrhagic detachment of the overlying RPE (Figs. 2 and 3). Several studies have provided evidence that local inflammatory mechanisms may add further damage to the RPE and Bruch's membrane and lead to the breakdown of their normal anatomic apposition.<sup>5,59,76,88,89</sup> Inflammatory involvement has been demonstrated in studies of excised CNV tissue of AMD patients,<sup>30,66,68,106</sup> and ingrowth of CNV into the sub-RPE space was suggested to be augmented by activated macrophages and other inflammatory cells that secrete enzymes and cytokines that degrade Bruch's membrane.

Another theory, proposed by Green et al,<sup>54</sup> relates to invasion of CNV through an already thickened Bruch's membrane and preexisting PED, suggesting that CNV may develop as a complication of PED, representing a continuum of a common underlying disease process. Marshall et al have proposed that PED may cause disruption of function of collagen type IV found normally in Bruch's membrane.<sup>79</sup> Thus, migration of endothelial cells into the collagenous zones of Bruch's membrane is allowed and the normal prevention of ingrowth of CNV is lost.

A significant contribution to our current concept of the pathogenesis of neovascularization and formation of vascularized PED was made in the past few years, when the importance of anastomotic connections between the retina and the choroidal circulation was introduced. Hartnett et al identified

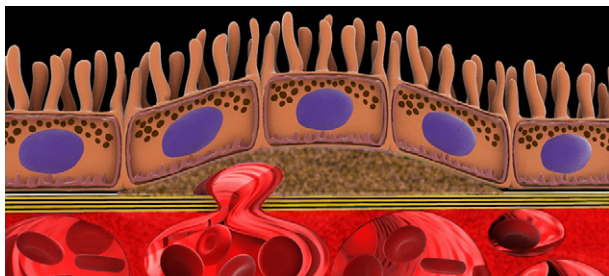


Fig. 2. Graphic illustration showing budding of choroidal neovascularization through Bruch's membrane, with exudation underneath the RPE that causes serous detachment of the RPE with its separation from the inner collagenous layer of Bruch's membrane.

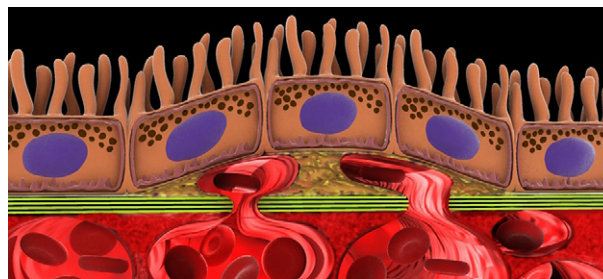


Fig. 3. Graphic illustration of fibrovascular PED. Choroidal neovascularization budding through Bruch's membrane causes elevation of the RPE.

PED associated with retinal angiomatous lesions among other PED types diagnosed in patients with AMD,<sup>60</sup> and have suggested that the retinal vascular abnormality may give rise to retino-choroidal anastomoses (RCA). Although the pathogenesis of these lesions is not fully understood, the authors suggested loss of RPE polarity as a possible pathogenic factor, by allowing retinal neovascular complexes to invade the RPE and become similar to choroidal vasculature. In a subsequent report by Kuhn et al, RCA were indicated as a frequent (93%) finding in patients with serous PED and occult CNV demonstrating hot spots on ICG, and the importance of RCA in evaluation of these patients was stressed.<sup>72</sup> In a study of the incidence of RCA in patients with occult CNV and their affect on response to laser treatment,<sup>112</sup> the nature of RCA was suggested to be probably retinal angiomatous proliferations, and these lesions were concluded as a possible primary event in formation of separation of the RPE and secondary ingrowth of CNV, although they may also be observed in eyes without associated PED. The previously mentioned studies probably strengthen the theory that development of neovascularization is a key event in the pathogenesis of detachment of the RPE.

## B. PATHOPHYSIOLOGY OF DRUSENOID PED

Drusenoid PED is another form of PED related to AMD. Drusen, deposits of neutral lipid within the extracellular material of Bruch's membrane, external to the basement membrane of the RPE have been shown to occur with age.<sup>12,76,91,101,107</sup> Histologically, Gass described deposits of extracellular material lying between the RPE basement membrane and the inner collagenous Bruch's membrane.<sup>43</sup> Typically, these deposits, termed *basal linear* drusen, occur in middle-aged patients and are considered to represent the earliest sign of AMD. A distinction should be made between basal linear deposits and *basal laminar* deposits, which are nodular thickenings of the RPE basement membrane<sup>101</sup>



and probably have a different pathogenesis. Basal laminar deposits appear clinically as small, round drusen evenly distributed in the posterior pole, have equal frequency in whites and non-whites, and predispose to formation of vitelliform macular detachment later in the 6<sup>th</sup> decade of life.<sup>43</sup> The present discussion refers to drusen associated with AMD, namely basal linear deposits.

Clinically, basal linear drusen are visible as yellow-white deposits lying deep to the retina in variable size and shape, are considered dynamic, exhibiting a natural process of increase and decrease in size, and may coalesce or regress.<sup>80</sup> Confluence of soft drusen, larger than 63  $\mu\text{m}$ , usually occurring in the central macula, probably predispose to formation of drusenoid PED,<sup>19,22,26,52</sup> whereas those with indistinct borders were found to have the highest rate of progression to confluence and advanced AMD.<sup>34,71</sup> The term *drusenoid PED* usually refers to lesions larger than 1,000  $\mu\text{m}$  in greatest length,<sup>19</sup> although the typical size is less than one disk diameter.<sup>17</sup> It has been hypothesized that accumulation of fluid due to the hydrophobic barrier created by the lipid deposition in Bruch's membrane may contribute to further enlargement of the detachment<sup>4,19</sup> (Fig. 4).

### III. Clinical and Angiographic Features

The different clinical entities of PED types associated with AMD<sup>12,22,60</sup> are distinct in many clinical and prognostic aspects, as will be discussed later, but they all share several basic similarities. In most instances, PED occurs asymptotically, but patients will report blurred vision, distortion, metamorphopsia, or micropsia when the fovea is involved. Induced hyperopia is another possible symptom. PED is detected on clinical examination as a single or multiple elevated mounds. Its size may vary from sub-bi-microscopic to several disk diameters or larger.<sup>43,73</sup> Pigmentary changes, such as

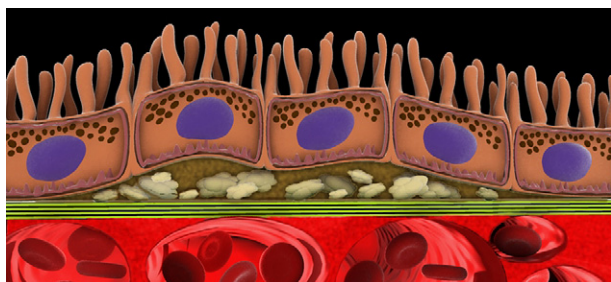


Fig. 4. Diagram illustrating the pathogenesis of drusenoid PED. Confluence of soft drusen, with secondary accumulation of fluid due to the hydrophobic barrier created by the lipid deposition in Bruch's membrane cause elevation of the RPE.

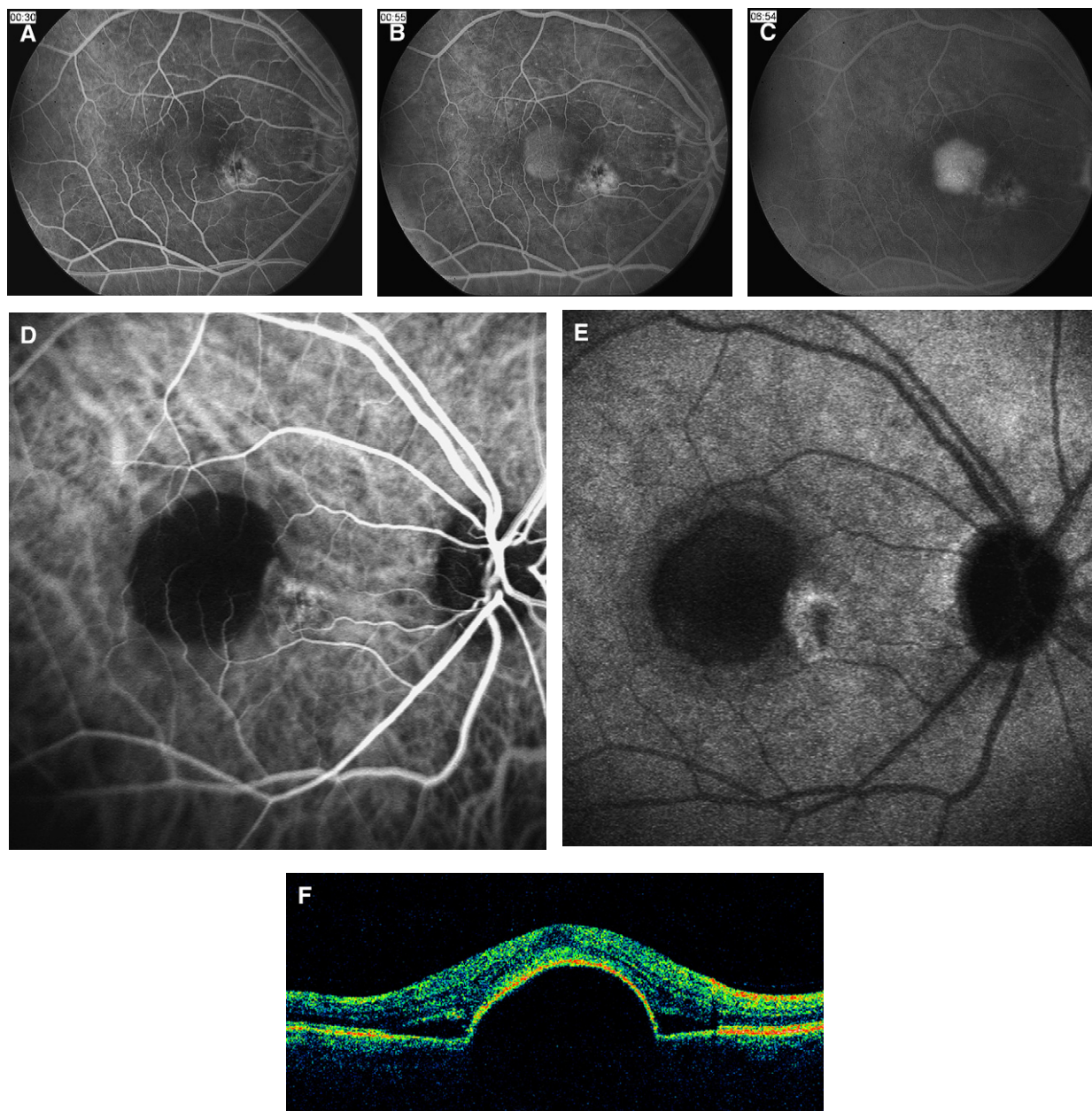
clumping or mottling, are common overlying PED. Orange pigment ring and pigment band on the dome, proposed by Yannuzzi<sup>126</sup> as a possible indicator of a chronic disease, were reported to be composed of melanin and lipofuscin.<sup>78</sup> Lipofuscin, belonging to a group of autofluorescent lipid-protein aggregates accumulating in post-mitotic RPE cells,<sup>134</sup> have been shown to parallel in amount and distribution to intensity of fundus autofluorescence.<sup>34,35,122</sup> As lipofuscin may induce apoptosis of the RPE cells,<sup>118</sup> the resultant fundus autofluorescence was suggested by Spaide<sup>114</sup> to be regarded as a possible sign of future oxidative injury.

Frequently, though not invariably, PED is a feature of an underlying CNV.<sup>37</sup> One clue to the presence of CNV beneath a PED could be an overlying serous retinal detachment arising as a result of disruption of the tight junctions between adjacent RPE cells. A shallow serous retinal detachment may overlie PED, however, even in the absence of CNV, although quite rarely.<sup>17,43</sup> Other possible findings indicating the presence of CNV underlying a PED include the presence of lipid and blood.<sup>16</sup> Chorio-retinal folds radiating from a serous PED were found to be another manifestation of CNV, because contraction of sub-RPE fibrovascular tissue causes folding of the overlying and intimately adherent RPE.<sup>103</sup>

In light of their similar ophthalmoscopic appearance, the importance of fluorescein angiography (FA) in more exacting evaluation of seemingly identical PED types and correct recognition of a co-existing CNV has long been recognized. The main clinical differences between distinct PED types, the accepted FA guidelines that had been drawn for their detection, as well as ICG angiography characteristics, are now described.

#### A. SEROUS PED

Serous PED is defined as an area of smooth, sharply demarcated dome-shaped and regular RPE elevation, often yellow-orange in color with reddish halo of subretinal fluid. It characteristically has sharply delineated margins, caused by the firm adherence of RPE to Bruch's membrane. The diagnosis of serous PED is made on FA, which reveals a rapid, bright, and uniform filling of the entire lesion, slightly later than background fluorescence, accumulating progressively and reaching a peak in very late frames<sup>8,43,126</sup> without leakage (Fig. 5). The intense hyperfluorescence that remains bright with sharply delineated borders in the late-phase frames is thought to be due to rapid diffusion of the fluorescein molecules across a permeable Bruch's membrane and pooling in the sub-RPE space.



*Fig. 5.* A: Fluorescein angiogram of the right eye, showing an early bright hyperfluorescence and an adjacent area of hyperfluorescence. B: Mid frame showing homogenous filling of the PED, with sharp borders. C: Late frame showing homogenous hyperfluorescence of serous PED. An area of hyperfluorescence is consistent with subretinal neovascularization associated with the PED. D: Early frame of ICG-Angiography of the same eye showing round hypofluorescence with sharply demarcated borders typical for serous PED. A nasal hot spot is consistent with CNV. E: Late ICG-angiography frame of the same eye. The round hypofluorescence remained with sharply demarcated borders, whereas the inferonasal hot spot intensified. F: 90° OCT scan, showing a large subfoveal smooth surface PED. There is minimal retinal detachment surrounding the PED. No intra-retinal edema is seen.

Serous PED is described as potentially obscuring the boundaries and thereby the extent of associated CNV, which is hence called occult in FA. Gass described a meniscus of blood or pigment at the dependent part of the PED,<sup>40</sup> as well as a notched or reniform figure, representing firm adherence between the CNV and overlying RPE, resulting in

detachment of the RPE at the margin of the CNV, as providing clues to the presence of an associated underlying CNV.

Digital indocyanine green videoangiography (ICGV) has been reported to provide enhanced definition of the choroidal vasculature and Bruch's membrane,<sup>55,56,128,129</sup> thus enabling better study of



PED. Because indocyanine green angiography (ICGA) affords better visualization of CNV beneath serous PED than FA, it is an important adjunct to the diagnosis and classification of patients with occult CNV associated with serous PED as demonstrated on FA.<sup>9,46,85,100,113,128,129</sup> Serous PED was described as a hypofluorescent lesion on ICGA, typically remaining hypofluorescent in all phases of the angiography<sup>129</sup> (Fig. 5), although others have found that serous PED could be hypofluorescent, isofluorescent, or even hyperfluorescent with respect to the background choroidal fluorescence during late stages, possibly as a result of lipid accumulation in Bruch's membrane.<sup>90</sup> Flower noted apparent fluorescence of fluid beneath PED in fundus camera early phase ICGV images that appeared to be attributable to serous fluid light-scatter arising from adjacent fluorescent structures,<sup>38</sup> probably as a consequence of the fundus camera optics and not due to the presence of dye.

Yannuzzi termed the appearance of a hyperfluorescent area in the early phase of ICGA with leakage in the late phase as *vascularized* PED associated with CNV.<sup>129</sup> He identified a *non-vascularized* type of PED as a round hypofluorescent area without spotty leakage, indicating the absence of an associated CNV (Fig. 6). In a subsequent report on ICGV examinations of patients with serous PED associated with occult CNV secondary to AMD evident on FA,<sup>128</sup> Yannuzzi defined 96% eyes as having a *vascularized* PED and further divided them into two groups. A solitary area of well-delineated CNV, demonstrated on ICGA as a bright hyperfluorescent lesion no larger than one disk area, was defined as *focal* CNV or hot spot (Fig. 7). A larger area of neovascularization with variable delineation, and usually with less intense fluorescence, was defined as *plaque* CNV. The remaining 4% of eyes in that study had no evidence of underlying CNV on ICGV. Similar results, confirming the superiority of ICGA in detecting CNV in patients with AMD-associated PED and its prognostic significance were subsequently reported by others.<sup>21,95,125</sup>

Several works have attempted to identify specific features of PED associated with hot spots. In their study of 125 AMD patients with CNV associated with serous PED, Hartnett et al found retinal vascular abnormalities displaying either a feeder retinal vessel or an emptying venule in nine of them (7.3%).<sup>60</sup> The recognized communication between the retinal vasculature and a deep retinal complex in PEDs was detected angiographically as a feeding retinal vessel dipping toward the outer retina, with a sub-RPE component and leakage in late phase. Kuhn et al analyzed eyes with vascularized PED with hot spots to identify specific features that could

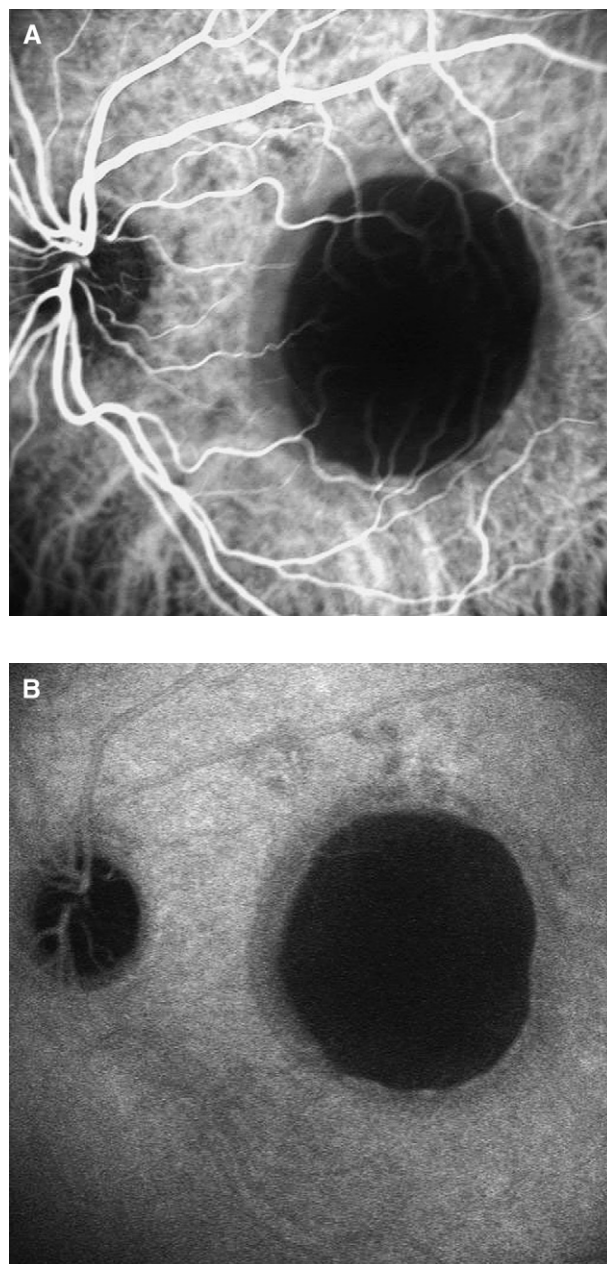


Fig. 6. A: ICG angiogram demonstrating round hypofluorescence with sharply lined borders consistent with serous PED. B: A late ICG-A frame showing absence of hyperfluorescent element, suggestive for non-vascularized serous PED.

explain the unfavorable natural history and poor response to laser treatment.<sup>72</sup> In 50 of 54 (93%) eyes, ICGV analysis showed anastomoses of mostly (90%) a single or double retinal vein with CNV within the hot spot. The development of RCA was concluded as probably of an acquired, unknown pathogenesis and specifically related to development of vascularized PED. Weinberger et al evaluated alterations in the retinal vasculature overlying both vascularized and non-vascularized PED in

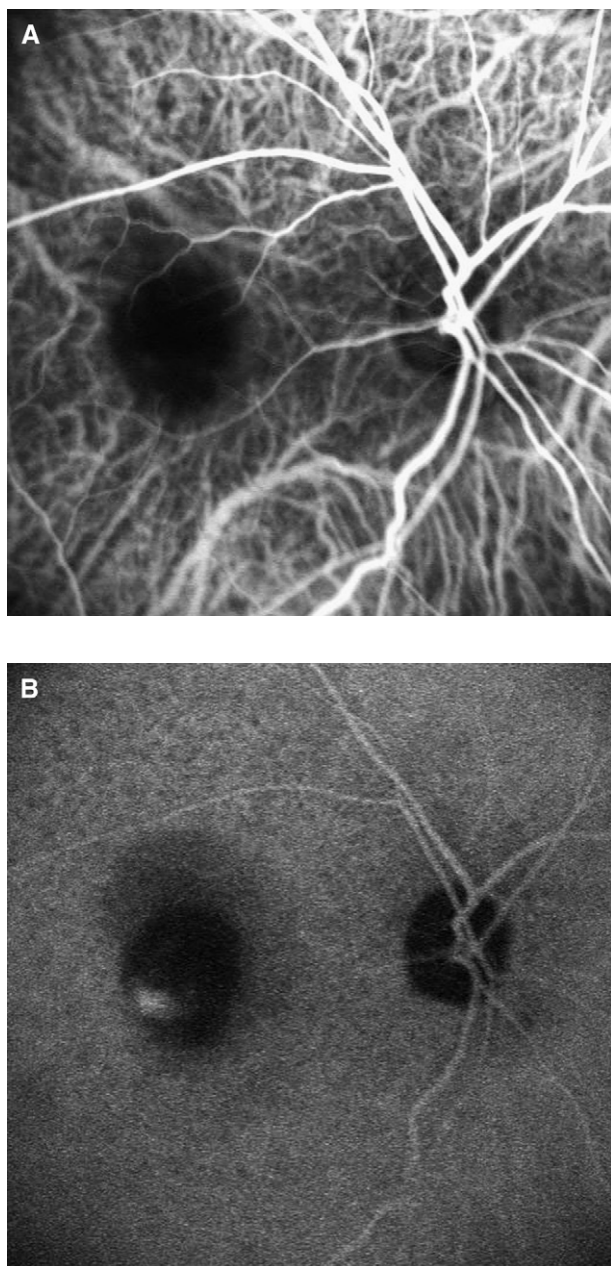


Fig. 7. A: ICG angiogram early frame of the right eye. A hyperfluorescent area within the round hypofluorescence is seen. B: Large area of leakage in the late phase representing a plaque CNV associated with serous PED.

neovascular AMD using ICGV and FA.<sup>124</sup> The detected retinal vasculopathy included microaneurysms, vascular leakage, and areas of non-perfusion. The abnormalities were significantly more detectable by ICGV than on FA, and their occurrence was directly correlated with presence of CNV. Iida et al stated that although the described retinal microangiopathies could be secondary to the longstanding macular detachment itself,<sup>67</sup> and not necessarily to the underlying pathology that caused

the PED, they usually represent underlying polypoidal CNV.

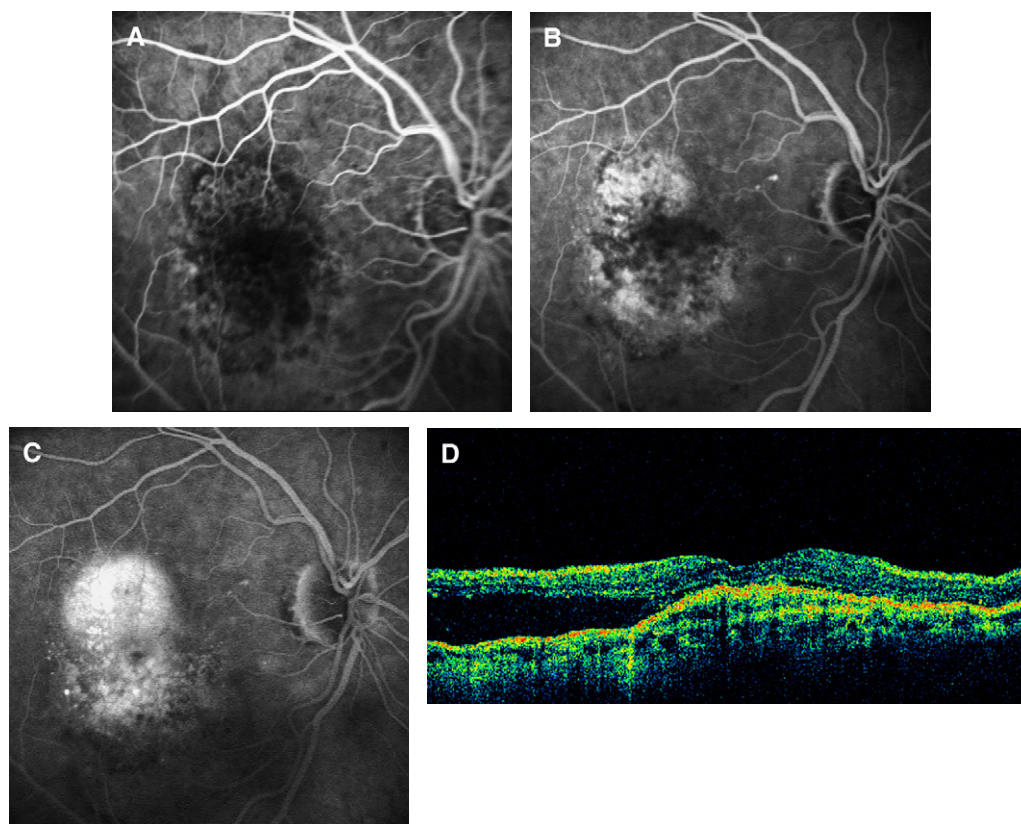
Slakter et al further evaluated the incidence of RCA in patients with occult CNV and hot spots on ICG to determine clinical and angiographic features indicating their presence.<sup>15</sup> They noted that RCA were present in 27% of patients with associated serous PED, as opposed to 13% in patients without PED. Most of the lesions were multiple anastomotic connections, and had at least one retinal vein involved. Clinical and angiographic features suggestive of presence of RCA included preretinal and intraretinal hemorrhage, cystoid macular edema, sudden termination of a retinal vessel, and serous PED in association with occult CNV with a hot spot at or near the retinal surface in the absence of a window defect evident on FA. On ICG, key features were focal hot spot adjacent to a serous PED and intraretinal late leakage surrounding neovascularization.

#### B. FIBROVASCULAR PED

Fibrovascular PED is a subset of occult CNV.<sup>17</sup> Fibrovascular PED was defined<sup>1</sup> as an area of irregular RPE elevation, best depicted on stereoscopic angiography, in contrast to the regular smooth-surfaced elevation of serous PED. The irregular elevation corresponds to an area of stippled or granular hyperfluorescence, which is not as bright as classic CNV and which emerges within 1–2 minutes of fluorescein injection (Fig. 8). Late-phase frames often reveal these areas to somewhat intensify in fluorescence and demonstrate persistent staining or leakage beyond the boundaries of fluorescence, the presence of elevation, or both, probably as a result of pooling in the subretinal space overlying the PED or entrapment within the fibrous tissue.<sup>17</sup> Such a pattern was deemed sufficient to confirm the diagnosis of occult CNV. Other FA features described in eyes with fibrovascular PED include tiny focal hyperfluorescent pinpoint spots at the level of the RPE, arising in mid and late frames, which do not correspond to drusen or foci of depigmentation, and becoming brighter and slightly larger on later frames. Scant overlying subretinal fluid may also sometimes be seen.<sup>39</sup>

As previously mentioned, ICGA is reported to provide more accurate definition of CNV underlying PED, thus allowing better appreciation of its precise nature and affording practical implications.<sup>57,125,126,128,129</sup> In several studies of ICGA features of occult CNV, PEDs with irregular hypofluorescence, or a hyperfluorescent “hot spot” were correlated closely with CNV, prompting





*Fig. 8.* A: FA of the right eye presenting a granular hyperfluorescence emerging within 30 seconds of fluorescein injection. B: Mid phase frame showing intensification of the granular hyperfluorescence. C: Late-phase frame, demonstrating intensification with leakage beyond the boundaries of early fluorescence. D: OCT picture 90-scan. PED with thickening of the RPE layer and breaks in its' continuity representing the CNV. Large sub-retinal and intraretinal fluid accumulation peripheral to PED.

recommendation for close follow-up.<sup>133</sup> Yannuzzi et al analyzed 1,000 eyes with occult CNV using digital ICGV.<sup>57,128</sup> As described earlier, the three angiographic types described were “hot spots” or focal CNV, plaque CNV, whether well- or ill-defined, and combination lesions. Plaque CNV was the most frequent finding, observed in 61% cases, and reported to occupy half or more of the area of the PED in 78% of the eyes.<sup>128</sup> Focal CNV was observed in 29% of the eyes, usually extrafoveal in location. Combination lesions were observed in 8% of the eyes.

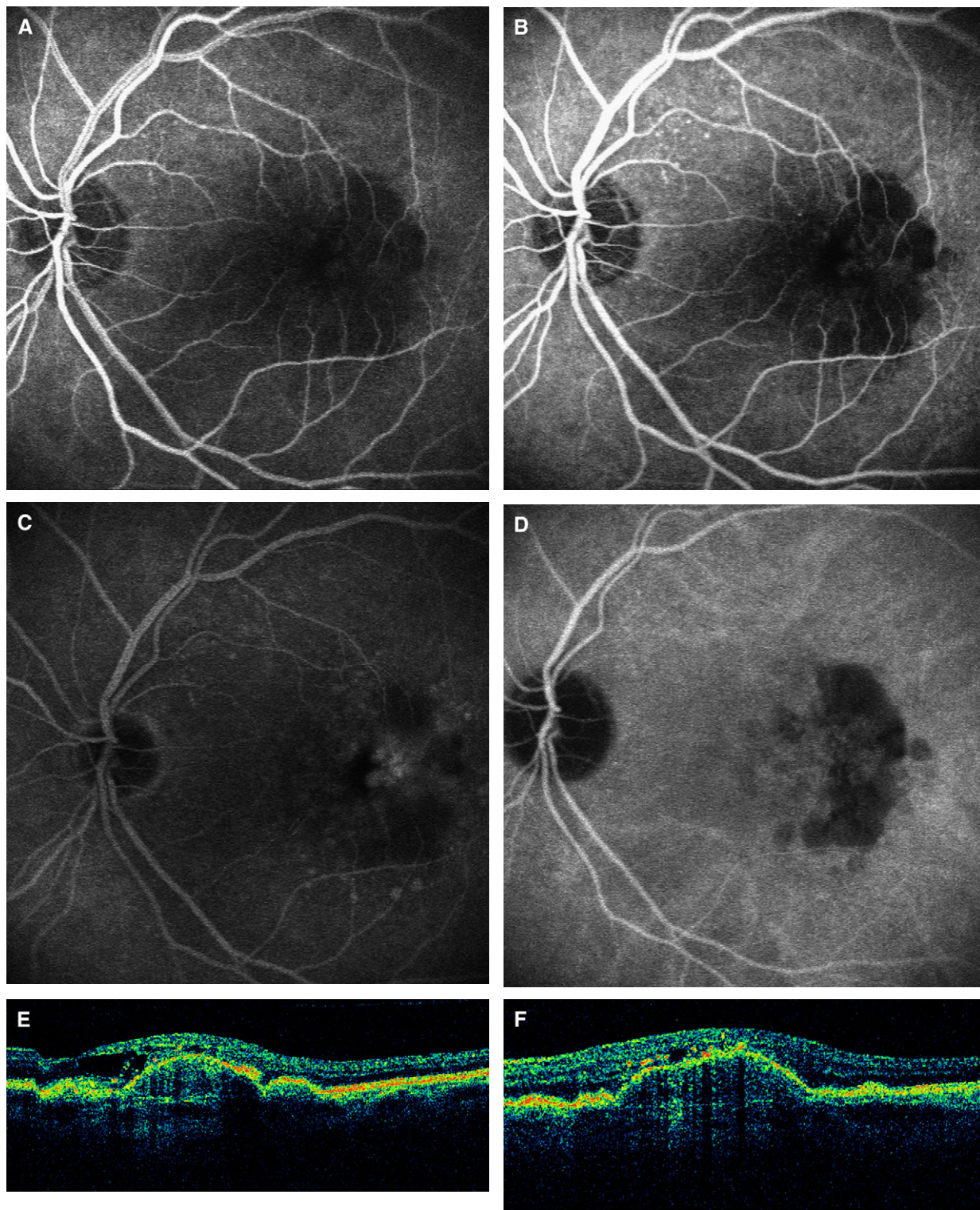
Haddad et al<sup>58</sup> have used the nomenclature proposed by Guyer and Yannuzzi<sup>55</sup> to classify fibrovascular PED, as noted on FA, on the basis of location of hot spot and plaque, and to evaluate the potential contribution of ICGA for determination of eligibility to treatment in eyes with AMD. Among 71 eyes with fibrovascular PED evident on FA, focal spots were noted in 39%, of which 31% were extra or juxtafoveal, plaques were present in 35%, and combination lesions were noted in 12%. Among all eyes with occult CNV examined within 15 days of symptoms, whether or not associated with

fibrovascular PED, focal spots were visualized in 49%, indicating that up to half eyes with occult CNV would be converted to well delineated focal spots by ICGA.

### C. DRUSENOID PED

Drusenoid PED, formed probably on the background of progressive enlargement and confluence of large soft drusen,<sup>12</sup> is described as an RPE detachment with scalloped borders and an irregular surface, often with overlying orange-gray radiating hyperpigmentation and typical slow rate of enlargement.<sup>17,43</sup> Roquet et al have analyzed the clinical features of drusenoid PED in AMD in 61 untreated eyes.<sup>99</sup> Bilaterality was noted in 91% of cases, and the most frequent symptom at first examination was metamorphopsia (40%). The characteristic FA hyperfluorescence outlined for drusenoid PED is gradual staining of the sub-RPE with no leakage and possible irregular density (Fig. 9).<sup>17,43,99</sup> The delayed hyperfluorescence is often sprinkled by hypofluorescent foci corresponding to pigment





*Fig. 9. A: Early frame FA showing a hypofluorescent area with scalloped borders and central element of irregular hyperfluorescence. B: In mid phase, gradual staining of the sub-RPE is noted. C: Delayed staining without leakage suggestive for drusenoid PED. D: ICG-A frame showing an area of hypofluorescence. E: OCT image horizontal scan. Three PEDs with homogenous hyper-reflectivity underneath. Small hyper-reflective small dots above the PED with shadowing below corresponding with pigmented changes. Neuroretinal cystic changes above the PED. No subretinal fluid is seen. F: Oblique scan. Small RPE elevations surrounding one large central PED corresponding with drusenoid PED. The RPE elevations are with solid hyper-reflective material. Small hyper-reflective areas above the elevations are pigmented lesions with a shadowing effect. No subretinal fluid is seen.*

deposits, and is usually smaller and shallower than fibrovascular PED.<sup>17</sup> ICGA was described in Riquet's work as very helpful in identifying and locating associated CNV, but to the best of our knowledge, no specific features of drusenoid PED on ICG have been described.

#### IV. Optical Coherence Tomographic Images

Optical coherence tomography (OCT), a non-invasive, non-contact, high-resolution scan of the retina based on the reflective properties of its layers, creates cross-sectional images, and has been used to study macular disease states, among which are detachments of the RPE. Drusenoid PED, tears of the RPE, and retinal angiomatous lesions were also identified as lesions effectively demonstrated with OCT.<sup>97,123</sup> The RPE, which is a highly reflective layer, appear red on OCT.

In the textbook of OCT of ocular disease,<sup>81</sup> the definition drawn for serous PED secondary to AMD is a localized, relatively pronounced dome-shaped elevation of the external high reflective band that appears scatter-free, optically empty with sharp margins sometimes associated with reflections from the deeper choroid (Fig. 5). Fibrovascular PED is described as a well-defined elevation of the RPE with a deeper area of backscattering corresponding to fibrous proliferation (Fig. 8). Drusenoid elevation is seen on OCT as an RPE elevation with homogenous hyper-reflective material underneath, in contrast with the hypo-reflectivity seen underneath the RPE in serous PED (Fig. 9). Usually more than one RPE elevation is noted and there is no surrounding subretinal fluid. The retina overlying drusenoid PED can appear normal or harbor cystic changes, with small pigmented clumps associated with shadowing effect.

Yoshida et al<sup>131</sup> classified 24 eyes with dome-like PED as seen ophthalmoscopically by OCT images to fall into two groups according to the presence or absence of a highly reflective line at the level of the RPE. In the first group, the same reflex was noted on OCT in the area of the PED as that seen in sub-RPE in other parts. Patients in this group demonstrated hyperfluorescence on FA, had smaller PEDs, and better VA. A partial or total highly reflective line at the level of the RPE over the PED defined the second group, in which irregular hyperfluorescence on FA, significantly larger PED, and lower VA were also noted. Although the authors did not state which group corresponds to which specific recognized PED type, it is agreed that PEDs in older patients tend to be associated with diffuse

degenerative changes. OCT was formerly reported to be unable to detect CNV beneath serous pigment epithelial detachments.<sup>61</sup> In a subsequent work, however, Sato et al<sup>102</sup> studied the tomographic features of 35 eyes with CNV judged angiographically to be within or at the margin of serous PED in AMD. The PED seemed to be a dome-shaped, optically empty space lined by a highly reflective RPE layer in all eyes. In 56% of 18 eyes in which the CNV involved the angiographic margin of the PED, a smaller PED was noted as being adjacent to it, with a tomographic notch between the central and small PEDs. In 76% of 17 eyes in which the CNV was within the PED, a notch was seen in the central mound, resulting in a double-mound contour. A tomographic notch in a serous PED was, therefore, suggested as being diagnostically important as an indication of CNV.

#### V. Natural Course

Although the natural course is different for each PED type, they all share a common potential outcome. Tearing of the RPE is a sight-threatening complication of PED that usually occurs at the junction between the detached and attached portions of the RPE.<sup>33,65</sup> The suggested pathogenesis is that a tangential shear force within the RPE causes dehiscence and separation of the epithelial basement membrane.<sup>8,42</sup> Vitreomacular traction in the foveal area, demonstrated by OCT, has been proposed as another potential mechanical contributor to ripping of the RPE.<sup>83</sup> Small areas of RPE thinning or small holes along the margins of PED have been proposed as characteristic signs of impending PED tears.<sup>109</sup> RPE rip has been described either spontaneously, with or without associated CNV,<sup>7,13,18,42,45,74,120,130</sup> after laser photocoagulation,<sup>41,42,119,130,132</sup> and after photodynamic therapy (PDT).<sup>44,47,94</sup> A study of angiographic pre-tear characteristics in 40 eyes with PED identified alterations in the filling pattern of the PED, the most noteworthy of which was uneven filling.<sup>28</sup> Following tearing, the ripped RPE rolls toward the opposite margin, leading to sudden exposure of a bare Bruch's membrane. A fibrous plaque typically resurfaces the bed of the tear, but it may sometimes remain stable or be replaced by new RPE.<sup>26,65</sup> In most described cases, the patients experienced profound decrease in visual acuity.<sup>26,33,41,42,51,65,83,104,119,130</sup> Several series have demonstrated significant risk of bilaterality, suggesting that specific alterations at the level of Bruch's membrane may predispose to this complication.<sup>25,87,104</sup>



### A. SEROUS PED

The prognosis in eyes with pigment epithelial detachments is probably related to the presence of associated CNV and the age of the patient.<sup>70</sup> Several retrospective studies have indicated that the overall risk for developing CNV within about 25 months after diagnosis among patients with serous PED associated with AMD is 24–34%.<sup>37,60,109</sup> Development of CNV was associated with a final VA of 20/200 or less.<sup>37</sup> Identified risk factors for developing CNV were age older than 60 years, a PED larger than 1 disk diameter, foveal involvement of the PED, and overlying sensory retinal detachment that did not decrease during follow-up.<sup>37,108</sup> Additional risk factors were notching, a hot spot, and irregular filling of the PED on ICG.<sup>37</sup>

In contrast, Pauleikhoff et al<sup>92</sup> characterized the natural clinical and visual course of serous PED in 101 elderly patients and concluded that all PEDs, whether vascular PED, avascular PED, or associated with polypoidal choroidal vasculopathy, had a similar clinical course with respect to visual loss and enlargement or regression. In another study of the natural course of fellow eyes of unilateral CNV secondary to AMD, the same author<sup>93</sup> reported that within 80 months of follow-up, patients with occult CNV with serous PED had a significantly higher risk of visual loss occurring in the second eye than of patients with CNV without PED. The annual risk of second eye involvement was increased after unilateral presentation.

Chang et al<sup>23</sup> also studied the predictive value of occult CNV associated with serous PED regarding the nature of CNV that develops in the fellow eye. They found significant symmetric distribution of type of CNV between eyes among patients with occult CNV secondary to AMD, whether associated with serous PED or not. It was suggested that eyes with occult CNV secondary to AMD could be classified by the presence or absence of an associated serous PED, and that such unilateral findings are important with respect to the natural history.

### B. FIBROVASCULAR PED

As defined by the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) and Verteporfin in Photodynamic Therapy (VIP) studies,<sup>8</sup> fibrovascular PED is actually one of two FA-recognized forms of occult CNV. Thus, it could be expected that the natural course and the visual outcome<sup>20</sup> of vascularized PED would be poor due to the development of classic CNV,<sup>122</sup> and ultimately, formation of a disciform scar or a tear of the RPE.<sup>37,58,60,82,96</sup>

Tears of the RPE are reported to occur in 10% of patients with serous PED secondary to AMD,<sup>22</sup> but CNV is considered one of the predisposing factors for tear formation in patients with PED.<sup>24,42</sup> A tendency to bilaterality has been reported.<sup>25</sup> Tears of the RPE are described as complicating PED and producing severe visual loss, especially when the macular area is involved.<sup>33,51</sup> As the free margin of the torn RPE rolls toward the opposite margin of the PED and undergoes subsequent shrinkage, a large bare area of Bruch's membrane is left, producing vision loss. Tears have been described to occur spontaneously,<sup>32,33</sup> after laser treatment,<sup>41,83,132</sup> and after PDT as well.<sup>44,47,94</sup>

Coscas et al<sup>28</sup> studied the characteristic angiographic changes of PED anteceding tear stage in 40 eyes. The most prominent feature observed was uneven filling of the PED, noted as a remarkably hypofluorescent central area that remained dark until late frames, or hyperfluorescence that appeared early at the margins of the PED, increased progressively, and sometimes demonstrated a crenated edge. Alterations in the filling pattern of the PED, including enlargement and modifications in its shape, development of notches, and the onset or increase of subretinal fluid, hard exudates, or hemorrhages were also noted and interpreted as characteristic preceding angiographic changes. The presence of these changes was suggested as an indication for high risk of tearing and careful consideration of laser treatment.

### C. DRUSENOID PED

It is commonly agreed that drusenoid PEDs are usually consistent with good vision, especially in early stages. Roquet et al<sup>99</sup> identified three natural outcomes of 61 eyes with drusenoid PED in AMD: persistence of drusenoid PED in 38%, development of geographic atrophy (GA) in 49%, and CNV in 13%. The 10-year occurrence rate was 75% for GA and 25% for CNV, indicating a better prognosis for drusenoid PED than for vascular PED. Hartnett<sup>60</sup> also obtained best visual prognosis and anatomic results for PED associated with confluent drusen: They included flattening of the PED in 15/21 eyes, development into a serous lesion in 1/21 eyes, and persistence without change in 5/21 eyes within 41 months. Those findings were in contrast with PED associated with neovascularization, which had the poorest visual results.<sup>60</sup>

## VI. Treatment Options

### A. SEROUS PED

In the past, certain cases of serous PEDs could be selected for laser treatment by one of three possible



techniques.<sup>3,31,62,77</sup> A grid pattern photocoagulation could be considered if there was persistence and progression of the PED with associated visual decline but no underlying CNV was present,<sup>127</sup> although no conclusive evidence that photocoagulation alters the natural course of this condition was noted.<sup>15</sup> In cases when an underlying CNV was suspected, total photocoagulation of the PED could be considered if the fovea could have been spared, with high reported success rate for flattening of the PED.<sup>62</sup> Finally, photocoagulation of extrafoveal CNV beneath or at the margin of a PED could be performed in order to resolve the exudation and stabilize or improve the vision.<sup>77</sup> However, with the advancement of imaging techniques and our improved ability to localize neovascularization beneath PED, most of the newly diagnosed patients with PED as a lesion component of advanced AMD are simply ineligible for such treatment options. As will be detailed subsequently, such patients are neither suitable for PDT as these lesions were excluded from the TAP study and VIP trial. Therefore, currently no treatment for serous PED is proven effective, nor are recommendations for treatment guidelines established.

The optimal treatment for serous vascularized PED also remains to be determined. The Macular Photocoagulation Study (MPS)<sup>2</sup> showed that argon or krypton laser photocoagulation of extra and juxta foveal CNV reduced the risk of severe visual loss at 5 years, and established treatment guidelines for eyes meeting those eligibility criteria. Eyes with PED as a lesion component, however, were excluded from the MPS study. In contrast with a few earlier descriptions,<sup>15</sup> several more recent reports in the literature have indicated limited visual success of laser photocoagulation of eyes with CNV associated with PED in AMD. Closure of CNV continuous with PED and subsequent collapse of the PED after FA-guided laser photocoagulation was described in 57% of 14 treated eyes,<sup>77</sup> of which 75% also had visual improvement. Progression of CNV into the fovea with resultant visual loss, however, occurred in 43%. Similarly, others<sup>62</sup> have observed anatomic collapse of PED in 81% of 21 treated eyes, and sustained visual improvement was obtained in 33% with a mean follow-up time of 27 months, suggesting that laser treatment might be beneficial. No difference was found between eyes with CNV associated with PED that were treated with FA-guided argon or krypton laser photocoagulation,<sup>111</sup> where vision improved or remained stable in 53% of the 124 treated eyes, with a mean follow-up of 16 months.

Based on the assumption that the enhanced ability of infrared light to demonstrate choroidal

vasculature due to its higher transmission through the RPE may facilitate visualization of CNV beneath PED, subsequent studies were carried out to evaluate the efficacy of ICG-guided laser photocoagulation of CNV associated with PED. Gomez-Ulla et al<sup>48</sup> reported anatomical and visual results of 11 eyes with CNV associated with PED that were treated with ICG-guided diode laser photocoagulation. There was complete closure with complete resolution of exudates and flattening of the detachment in 5 (45%) eyes. The VA tested in the final examination improved or remained stable in 6 (55%) eyes, indicating that diode laser may be at least as effective as conventional laser with a shorter wavelength. Others<sup>14</sup> also noted that ICG-guided laser photocoagulation may improve or stabilize visual acuity in some eyes with FA evidence of occult CNV with PED. Several other works, however, indicated that ICG-guided laser photocoagulation in eyes with CNV associated with serous PED secondary to AMD does not appear to improve VA compared to observation.<sup>9,75</sup>

Axer-Siegel et al<sup>6</sup> were the first to report on the visual and anatomic outcome of patients with subfoveal occult CNV associated with serous PED of at least 1 disk diameter who were treated with PDT. In their patient cohort, 19 (56%) treated eyes lost 3 or more lines of VA, 7 (21%) lost 1 or 2 lines, 6 (18%) maintained their initial acuity and 2 eyes (6%) gained 1 or 2 lines. Severe visual loss occurred in 4 eyes (11%), however, due to subretinal hemorrhage or tear of the RPE, warranting further search of treatment modalities for eyes with CNV associated with serous PED.

Another treatment modality, described recently by Costa et al<sup>29</sup> as a pilot trial, is photothrombosis at the neovascular ingrowth site using ICG injection followed by laser application. Occlusion of the feeder vessel with cessation of leakage, restoration of macular architecture and visual improvement were induced in two patients with CNV associated with PED.

## B. FIBROVASCULAR PED

The AMD arm of the VIP trial<sup>1</sup> investigated whether PDT could safely reduce the risk of vision loss in patients with subfoveal occult with no classic CNV who have presumed recent disease progression. Occult CNV was defined as one of two possible fluorescent patterns on FA: The first, fibrovascular PED, was described as irregular elevation of the RPE that showed stippled or non-homogenous hyperfluorescence, usually within 1-2 minutes of injection, with boundaries that could be well or poorly demarcated and with persistent staining or late

leakage. The results from the VIP trial indicated that PDT could significantly reduce the risk of moderate and severe vision loss among patients with subfoveal occult CNV, because 121 (54%) treated eyes compared with 76 (67%) eyes in the placebo (control) group lost at least 15 letters, whereas 67 (30%) of the treated patients versus 54 (47%) of the controls lost at least 30 letters by 24 months. A subgroup analysis revealed that a greater benefit was achieved in lesions smaller than 4 disk areas or less and for lower levels of VA (i.e., a letter score of less than 65).

In the same study, 10/225 patients with AMD in the treated group versus none in the control group reported severe visual loss of 20 letters compared with pre treatment acuity within 7 days after treatment. Eight of them had occult with no classic CNV at baseline examination. The presumed causes for these events were presence of sub RPE blood in 3/10, extensive sub RPE fluid in 1/10, and in 6/10 no obvious cause could be found.

Recently, the use of intravitreal pegaptanib, an anti-vascular endothelial growth factor, was evaluated in the treatment of neovascular AMD in a prospective multicenter double-blind controlled clinical trial.<sup>49</sup> Inclusion criteria included patients 50 years of age and older with all angiographic subtypes of subfoveal CNV secondary to AMD and VA in the range of 20/40 to 20/320 in the study eye and 20/800 or better in the second eye. One of three possible doses of intravitreal pegaptanib was administered every 6 weeks over 48 weeks. All three doses of pegaptanib were reported as effective in reducing risk of moderate and severe visual loss as well as increasing chance of maintaining or gaining of visual acuity in comparison with control. No evidence was found that any angiographic subtype, lesion size of CNV, or level of baseline VA precluded a treatment benefit. Although the long-term safety of pegaptanib therapy is not yet known, it appears to be effective for CNV secondary to AMD, and widening use of this new treatment modality is expected to gain popularity in the near future.

### C. DRUSENOID PED

The rapid progression of neovascular AMD makes detection in its early stage likely to play a vital role in reducing the chance of severe visual loss. Therefore, for people over 65 years of age, the American Academy of Ophthalmology recommends an eye examination every 2 years, and it is commonly agreed that people over 50 years of age should have regular eye examinations and carry out self-monitoring tests using the Amsler grid.<sup>110</sup> Our in-

depth literature search yielded no publications on treatment options specific for drusenoid PED.

## VII. Summary

PED is a prominent clinical manifestation of what appears to be multiple disease processes. It often contributes to loss of central vision, whether or not it is related to the presence of CNV. The clinical finding of single or multiple elevated mounds could be related to one of several different entities and is an indication to perform angiography with fluorescein and indocyanine green. Serous PED, the type that demonstrates intense regular hyperfluorescence that remains bright with sharp borders in late frames, is described as potentially obscuring an underlying CNV. Although several case series have observed anatomic collapse of PED associated with CNV after treatment with argon or krypton laser, universal treatment guidelines have yet to be determined and randomized clinical trials are needed in order to establish the efficacy and safety of treatment protocols of these lesions. On the other hand, the fibrovascular type of PED, defined as an area of irregular elevation corresponding to granular hyperfluorescence with persistent staining or leakage in late frames, is one of two recognized forms of occult CNV that warrants PDT when it is subfoveal. Therefore, correct recognition of the various types of PED that are possible in AMD is essential for correct prognosis and treatment recommendations.

## VIII. Method of Literature Search

A thorough search of MEDLINE with PubMed was conducted for the words: *retinal pigment epithelium detachment, retinal pigment epithelium detachment and age-related macular degeneration, PED and retinal pigment epithelium detachment, fluorescein angiography and retinal pigment epithelium detachment, indocyanine green and retinal pigment epithelium detachment, choroidal neovascularization, optical coherence tomography and age-related macular degeneration, PED and photodynamic therapy, pegapanib, PED and retino choroidal anastomoses*. All years were searched (through 2006). All articles relating to PED in relation to AMD were included. Articles in foreign language with abstracts in English were included as well.

## References

1. \_\_\_\_: Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with

- ocult with no classic choroidal neovascularization—verteporfin in photodynamic ther. *Am J Ophthalmol* 131:541–60, 2001
2. \_\_\_\_: Subfoveal neovascular lesions in age-related macular degeneration. Guidelines for evaluation and treatment in the macular photocoagulation study. Macular Photocoagulation Study Group. *Arch Ophthalmol* 109:1242–57, 1991
  3. \_\_\_\_: Retinal pigment epithelial detachments in the elderly: a controlled trial of argon laser photocoagulation. *Br J Ophthalmol* 66:1–16, 1982
  4. Abdelsalam A, Del Priore L, Zarbin MA: Drusen in age-related macular degeneration: pathogenesis, natural course, and laser photocoagulation-induced regression. *Surv Ophthalmol* 44:1–29, 1999
  5. Anderson DH, Mullins RF, Hageman GS, et al: A role for local inflammation in the formation of drusen in the aging eye. *Am J Ophthalmol* 134:411–31, 2002
  6. Axer-Siegel R, Ehrlich R, Rosenblatt I, et al: Photodynamic therapy for occult choroidal neovascularization with pigment epithelium detachment in age-related macular degeneration. *Arch Ophthalmol* 122:453–9, 2004
  7. Axer-Siegel R, Lichter H, Rosenblatt I, et al: Simultaneous indocyanine green and fluorescein angiography in retinal pigment epithelium tear using the confocal scanning laser ophthalmoscope. *Am J Ophthalmol* 128:331–9, 1999
  8. Barbazetto I, Burdan A, Bressler NM, et al: Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment—TAP and VIP report No. 2. *Arch Ophthalmol* 121:1253–68, 2003
  9. Bauml CR, Reichel E, Duker JS, et al: Indocyanine green hyperfluorescence associated with serous retinal pigment epithelial detachment in age-related macular degeneration. *Ophthalmology* 104:761–9, 1997
  10. Bird AC: Bruch's membrane change with age. *Br J Ophthalmol* 76:166–8, 1992
  11. Bird AC: Doyne Lecture. Pathogenesis of retinal pigment epithelial detachment in the elderly; the relevance of Bruch's membrane change. *Eye* 5:1–12, 1991
  12. Bird AC, Marshall J: Retinal pigment epithelial detachments in the elderly. *Trans Ophthalmol Soc UK* 105:674–82, 1986
  13. Boguszaková J, Dubská Z: [Tears of the retinal pigment epithelium]. *Cesk Slov Oftalmol* 57:367–71, 2001
  14. Brancato R, Intorino U, Bolognesi G, et al: ICGA-guided laser photocoagulation of occult choroidal neovascularization in age-related macular degeneration. Indocyanine green angiography. *Retina* 20:134–42, 2000
  15. Braunstein RA, Gass JD: Serous detachments of the retinal pigment epithelium in patients with senile macular disease. *Am J Ophthalmol* 88:652–60, 1979
  16. Bressler NM, Bressler SB, Fine SL: Age-related macular degeneration. *Surv Ophthalmol* 32:375–413, 1988
  17. Bressler NM, Bressler SB, Fine SL: Neovascular (exudative) age-related macular degeneration, in Ryan SJ (ed): *Retina*. St. Louis, Mosby, ed 3 2001. chap 66, pp 1100–35
  18. Bressler NM, Finklestein D, Sunness JS, et al: Retinal pigment epithelial tears through the fovea with preservation of good visual acuity. *Arch Ophthalmol* 108:1694–7, 1990
  19. Bressler NM, Silva JC, Bressler SB, et al: Clinicopathologic correlation of drusen and retinal pigment epithelial abnormalities in age-related macular degeneration. *Retina* 14:130–42, 1994
  20. Bressler SB, Bressler NM, Fine SL, et al: Natural course of choroidal neovascular membranes within the foveal avascular zone in senile macular degeneration. *Am J Ophthalmol* 93:157–63, 1982
  21. Brumm G, Spital G, Radermacher M, et al: [Pigment epithelial detachments in age-related macular degeneration—classification, differentiation and prognosis]. *Klin Monatsbl Augenheilkd* 219:791–6, 2002
  22. Casswell AG, Kohen D, Bird AC: Retinal pigment epithelial detachments in the elderly: classification and outcome. *Br J Ophthalmol* 69:397–403, 1985
  23. Chang B, Yannuzzi LA, Ladas ID, et al: Choroidal neovascularization in second eyes of patients with unilateral exudative age-related macular degeneration. *Ophthalmology* 102:1380–6, 1995
  24. Chuang EL, Bird AC: The pathogenesis of tears of the retinal pigment epithelium. *Am J Ophthalmol* 105:285–90, 1988
  25. Chuang EL, Bird AC: Bilaterality of tears of the retinal pigment epithelium. *Br J Ophthalmol* 72:918–20, 1988
  26. Chuang EL, Bird AC: Repair after tears of the retinal pigment epithelium. *Eye* 2(Pt 1):106–13, 1988
  27. Ciardell AP, Guyer DR, Spitznas M, Yannuzzi LA: Central serous chorioretinopathy, in Ryan SJ (ed): *Retina*. St. Louis, Mosby, ed 3 2001. chap 68, pp 1153–81
  28. Coscas G, Koenig F, Soubrane G: The pretear characteristics of pigment epithelial detachments. A study of 40 eyes. *Arch Ophthalmol* 108:1687–93, 1990
  29. Costa RA, Rocha KM, Calucci D, et al: Neovascular ingrowth site photothrombosis in choroidal neovascularization associated with retinal pigment epithelial detachment. *Graefes Arch Clin Exp Ophthalmol* 241:245–50, 2003
  30. Dastgheib K, Green WR: Granulomatous reaction to Bruch's membrane in age-related macular degeneration. *Arch Ophthalmol* 112:813–8, 1994
  31. de Jong PT: Laser treatment of central serous chorioretinopathy, of pigment epithelial detachments and of subretinal neovascularizations in senile disciform macular degeneration. *Bull Soc Belge Ophthalmol* 197:55–61, 1981
  32. De Laey JJ, Riems D: Ripping of detached retinal pigment epithelium in senile macular degeneration. *Bull Soc Belge Ophthalmol* 207:27–35, 1983
  33. Decker WL, Sanborn GE, Ridley M, et al: Retinal pigment epithelial tears. *Ophthalmology* 90:507–12, 1983
  34. Delori FC, Dorey CK, Staurengi G, et al: In vivo fluorescence of the ocular fundus exhibits retinal pigment epithelium lipofuscin characteristics. *Invest Ophthalmol Vis Sci* 36:718–29, 1995
  35. Delori FC, Goger DG, Dorey CK: Age-related accumulation and spatial distribution of lipofuscin in RPE of normal subjects. *Invest Ophthalmol Vis Sci* 42:1855–66, 2001
  36. Eagle RC: Mechanisms of maculopathy. *Ophthalmology* 91:613–25, 1984
  37. Elman MJ, Fine SL, Murphy RP, et al: The natural history of serous retinal pigment epithelium detachment in patients with age-related macular degeneration. *Ophthalmology* 93:224–30, 1986
  38. Flower RW, Csaky KG, Murphy RP: Disparity between fundus camera and scanning laser ophthalmoscope indocyanine green imaging of retinal pigment epithelium detachments. *Retina* 18:260–8, 1998
  39. Frederick AR, Morley MG, Topping TM, et al: The appearance of stippled retinal pigment epithelial detachments. A sign of occult choroidal neovascularization in age-related macular degeneration. *Retina* 13:3–7, 1993
  40. Gass JD: Serous retinal pigment epithelial detachment with a notch. A sign of occult choroidal neovascularization. *Retina* 4:205–20, 1984
  41. Gass JD: Retinal pigment epithelial rip during krypton red laser photocoagulation. *Am J Ophthalmol* 98:700–6, 1984
  42. Gass JD: Pathogenesis of tears of the retinal pigment epithelium. *Br J Ophthalmol* 68:513–9, 1984
  43. Gass JDM: *Stereoscopic Atlas of Macular Disease: Diagnosis and Management*. ed 4. St. Louis, Mosby, ed 4 1997. pp 24–6 and 82–7
  44. Gelissen F, Inhoffen W, Partsch M, et al: Retinal pigment epithelial tear after photodynamic therapy for choroidal neovascularization. *Am J Ophthalmol* 131:518–20, 2001
  45. Gelissen F, Schneider U, Inhoffen W, et al: Indocyanine green angiography in retinal pigment epithelial tear. *Acta Ophthalmol Scand* 76:384–5, 1998
  46. Giovannini A, Scassellati-Sforzolini B, D'Altobrando E, et al: Choroidal findings in the course of idiopathic serous



- pigment epithelium detachment detected by indocyanine green videoangiography. *Retina* 17:286-93, 1997
47. Goldstein M, Heilweil G, Barak A, et al: Retinal pigment epithelial tear following photodynamic therapy for choroidal neovascularization secondary to AMD. *Eye* 19:1315-24, 2005
  48. Gomez-Ulla F, Gonzalez F, Abelenda D, et al: Diode laser photocoagulation of choroidal neovascularization associated with retinal pigment epithelial detachment. *Acta Ophthalmol Scand* 79:39-44, 2001
  49. Gragoudas ES, Adamis AP, Cunningham ET, et al: Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 351:2805-16, 2004
  50. Green K, Paterson CA, Cheeks L, et al: Ocular blood flow and vascular permeability in endotoxin-induced inflammation. *Ophthalmic Res* 22:287-94, 1990
  51. Green SN, Yarian D: Acute tear of the retinal pigment epithelium. *Retina* 3:16-20, 1983
  52. Green WR, Enger C: Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. *Ophthalmology* 100:1519-35, 1993
  53. Green WR, Key SN: Senile macular degeneration: a histopathologic study. *Trans Am Ophthalmol Soc* 75:180-254, 1977
  54. Green WR, McDonnell PJ, Yeo JH: Pathologic features of senile macular degeneration. *Ophthalmology* 92:615-27, 1985
  55. Guyer DR, Yannuzzi LA, Slakter JS, et al: Classification of choroidal neovascularization by digital indocyanine green videoangiography. *Ophthalmology* 103:2054-60, 1996
  56. Guyer DR, Yannuzzi LA, Slakter JS, et al: Digital indocyanine-green videoangiography of occult choroidal neovascularization. *Ophthalmology* 101:1727-35, discussion 1735-7, 1994
  57. Guyer DR, Yannuzzi LA: Occult choroidal neovascularization, in Yannuzzi LA, Flower RW, Slakter JS (eds): *Indocyanine Green Angiography*. St. Louis, Mosby, 1997, pp 157-80
  58. Haddad WM, Coscas G, Soubrane G: Eligibility for treatment and angiographic features at the early stage of exudative age related macular degeneration. *Br J Ophthalmol* 86:663-9, 2002
  59. Hageman GS, Luthert PJ, Victor Chong NH, et al: An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. *Prog Retin Eye Res* 20:705-32, 2001
  60. Hartnett ME, Weiter JJ, Garsd A, et al: Classification of retinal pigment epithelial detachments associated with drusen. *Graefes Arch Clin Exp Ophthalmol* 230:11-9, 1992
  61. Hee MR, Bauman CR, Puliafito CA, et al: Optical coherence tomography of age-related macular degeneration and choroidal neovascularization. *Ophthalmology* 103:1260-70, 1996
  62. Ho PC, Namperumalsamy P, Pruett RC: Photocoagulation of serous detachments of the retinal pigment epithelium in patients with senile macular disease. *Ann Ophthalmol* 16:213-8, 1984
  63. Holz FG, Pauleikhoff D, Klein R, et al: Pathogenesis of lesions in late age-related macular disease. *Am J Ophthalmol* 137:504-10, 2004
  64. Holz FG, Sheraidah G, Pauleikhoff D, et al: Analysis of lipid deposits extracted from human macular and peripheral Bruch's membrane. *Arch Ophthalmol* 112:402-6, 1994
  65. Hoskin A, Bird AC, Sehmi K: Tears of detached retinal pigment epithelium. *Br J Ophthalmol* 65:417-22, 1981
  66. Hutchinsonson AK, Grossniklaus HE, Capone A: Giant-cell reaction in surgically excised subretinal neovascular membrane. *Arch Ophthalmol* 111:734-5, 1993
  67. Iida T, Yannuzzi LA, Freund KB, et al: Retinal angiopathy and polypoidal choroidal vasculopathy. *Retina* 22:455-63, 2002
  68. Killingsworth MC, Sarks JP, Sarks SH: Macrophages related to Bruch's membrane in age-related macular degeneration. *Eye* 4:613-21, 1990
  69. Kirchhof B, Ryan SJ: Differential permeance of retina and retinal pigment epithelium to water: implications for retinal adhesion. *Int Ophthalmol* 17:19-22, 1993
  70. Klein ML, Obertynski H, Patz A, et al: Follow-up study of detachment of the retinal pigment epithelium. *Br J Ophthalmol* 64:412-6, 1980
  71. Klein R, Klein BE, Jensen SC, et al: The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* 104:7-21, 1997
  72. Kuhn D, Meunier I, Soubrane G, et al: Imaging of chorioretinal anastomoses in vascularized retinal pigment epithelium detachments. *Arch Ophthalmol* 113:1392-8, 1995
  73. Kunze C, Elsner AE, Beausencourt E, et al: Spatial extent of pigment epithelial detachments in age-related macular degeneration. *Ophthalmology* 106:1830-40, 1999
  74. Lafaut BA, Aisenbrey S, Vanden Broecke C, et al: Clinicopathological correlation of retinal pigment epithelial tears in exudative age related macular degeneration: pretear, tear, and scarred tear. *Br J Ophthalmol* 85:454-60, 2001
  75. Lim JI, Aaberg TM, Capone A, et al: Indocyanine green angiography-guided photocoagulation of choroidal neovascularization associated with retinal pigment epithelial detachment. *Am J Ophthalmol* 123:524-32, 1997
  76. Löffler KU, Lee WR: Basal linear deposit in the human macula. *Graefes Arch Clin Exp Ophthalmol* 224:493-501, 1986
  77. Maguire JI, Benson WE, Brown GC: Treatment of foveal pigment epithelial detachments with contiguous extrafoveal choroidal neovascular membranes. *Am J Ophthalmol* 109:523-9, 1990
  78. Marmor MF: Structure, function, and disease of the retinal pigment epithelium, in Marmor MF, Wolfensberger TJ (eds): *The Retinal Pigment Epithelium*. New York, Oxford University Press, 1998, pp 3-9
  79. Marshall GE, Konstas AG, Reid GG, et al: Collagens in the aged human macula. *Graefes Arch Clin Exp Ophthalmol* 232:133-40, 1994
  80. Marshall J, Hussain AA, Starita C, et al: Aging and Bruch's membrane, in Marmor MF, Wolfensberger TJ (eds): *The Retinal Pigment Epithelium*. New York, Oxford University Press, 1998, pp 669-92
  81. Mavrofrides EC, Villate N, Rosenfeld PJ, Puliafito CA: Age-related macular degeneration, in Schuman JS, Puliafito CA, Fujimoto JG (eds): *Optical coherence tomography of ocular diseases*. Thorofare, Slack Press, pp 243-6
  82. Meredith TA, Braley RE, Aaberg TM: Natural history of serous detachments of the retinal pigment epithelium. *Am J Ophthalmol* 88:643-51, 1979
  83. Meyer CH, Toth CA: Retinal pigment epithelial tear with vitreomacular attachment: a novel pathogenic feature. *Graefes Arch Clin Exp Ophthalmol* 239:325-33, 2001
  84. Moore DJ, Hussain AA, Marshall J: Age-related variation in the hydraulic conductivity of Bruch's membrane. *Invest Ophthalmol Vis Sci* 36:1290-7, 1995
  85. Müller C, Spital G, Radermacher M, et al: [Pigment epithelium detachments in AMD (age-associated macular degeneration) and "polypoidal choroidal vasculopathy". A fluorescein and indocyanine green angiography study]. *Ophthalmologie* 99:85-9, 2002
  86. Murphy RP, Yeo JH, Green WR, et al: Dehiscences of the pigment epithelium. *Trans Am Ophthalmol Soc* 83:63-81, 1985
  87. Norose K, Tanino T, Segawa K: Bilateral tears of the retinal pigment epithelium. *Br J Ophthalmol* 72:621-7, 1988
  88. Oh H, Takagi H, Takagi C, et al: The potential angiogenic role of macrophages in the formation of choroidal neovascular membranes. *Invest Ophthalmol Vis Sci* 40:1891-8, 1999
  89. Otani A, Takagi H, Oh H, et al: Expressions of angiopoietins and Tie2 in human choroidal neovascular membranes. *Invest Ophthalmol Vis Sci* 40:1912-20, 1999
  90. Parodi MB, Saviano S, Bondel E, et al: Hyperfluorescence associated with serous retinal pigment epithelial

- detachment on indocyanine green angiography. *Acta Ophthalmol Scand* 78:443-7, 2000
91. Pauleikhoff D, Harper CA, Marshall J, et al: Aging changes in Bruch's membrane. A histochemical and morphologic study. *Ophthalmology* 97:171-8, 1990
  92. Pauleikhoff D, Löffert D, Spital G, et al: Pigment epithelial detachment in the elderly. Clinical differentiation, natural course and pathogenetic implications. *Graefes Arch Clin Exp Ophthalmol* 240:533-8, 2002
  93. Pauleikhoff D, Radermacher M, Spital G, et al: Visual prognosis of second eyes in patients with unilateral late exudative age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 240:539-42, 2002
  94. Pece A, Introini U, Bottoni F, et al: Acute retinal pigment epithelial tear after photodynamic therapy. *Retina* 21:661-5, 2001
  95. Pece A, Introini U, Bolognesi G, et al: Indocyanine green angiography in age-related macular degeneration with occult neovascularization. *Ophthalmologica* 212:295-300, 1998
  96. Poliner LS, Olk RJ, Burgess D, et al: Natural history of retinal pigment epithelial detachments in age-related macular degeneration. *Ophthalmology* 93:543-51, 1986
  97. Puliafito CA, Hee MR, Lin CP, et al: Imaging of macular diseases with optical coherence tomography. *Ophthalmology* 102:217-29, 1995
  98. Ramrattan RS, van der Schaft TL, Mooy CM, et al: Morphometric analysis of Bruch's membrane, the choriocapillaris, and the choroid in aging. *Invest Ophthalmol Vis Sci* 35:2857-64, 1994
  99. Roquet W, Roudot-Thoraval F, Coscas G, et al: Clinical features of drusenoid pigment epithelial detachment in age related macular degeneration. *Br J Ophthalmol* 88: 638-42, 2004
  100. Sallet G, Lafaut BA, De Laey JJ: Indocyanine green angiography and age-related serous pigment epithelial detachment. *Graefes Arch Clin Exp Ophthalmol* 234:25-33, 1996
  101. Sarks SH, Sarks JP: Age related maculopathy: non-neovascular age-related macular degeneration and the evolution of geographic atrophy, in Stephen Ryan (ed): *Retina*. St. Louis, Mosby, ed 3 2001, pp 1064-99
  102. Sato T, Iida T, Hagimura N, et al: Correlation of optical coherence tomography with angiography in retinal pigment epithelial detachment associated with age-related macular degeneration. *Retina* 24:910-4, 2004
  103. Schatz H, McDonald HR, Johnson RN: Retinal pigment epithelial folds associated with retinal pigment epithelial detachment in macular degeneration. *Ophthalmology* 97: 658-65, 1990
  104. Schoepfner G, Chuang EL, Bird AC: The risk of fellow eye visual loss with unilateral retinal pigment epithelial tears. *Am J Ophthalmol* 108:683-5, 1989
  105. Schwartz SG, Guyer DR, Yannuzzi LA: Age-related retinal pigment epithelial detachments, in Marmor MF, Wolfensberger TJ (eds): *The Retinal Pigment Epithelium*. New York, Oxford University Press, 1998, pp 706-15
  106. Seregard S, Algvere PV, Berglin L: Immunohistochemical characterization of surgically removed subfoveal fibrovascular membranes. *Graefes Arch Clin Exp Ophthalmol* 232: 325-9, 1994
  107. Sheraidah G, Steinmetz R, Maguire J, et al: Correlation between lipids extracted from Bruch's membrane and age. *Ophthalmology* 100:47-51, 1993
  108. Shirakashi A: [The natural history of serous retinal pigment epithelial detachment]. *Nippon Ganka Gakkai Zasshi* 96:677-82, 1992
  109. Shiraki K, Kohno T, Ataka S, et al: Thinning and small holes at an impending tear of a retinal pigment epithelial detachment. *Graefes Arch Clin Exp Ophthalmol* 239:430-6, 2001
  110. Sickenberg M: Early detection, diagnosis and management of choroidal neovascularization in age-related macular degeneration: the role of ophthalmologists. *Ophthalmologica* 215:247-53, 2001
  111. Singerman LJ: Laser photocoagulation for choroidal new vessel membrane complicating age-related macular degeneration associated with pigment epithelial detachment. *Retina* 8:115-21, 1988
  112. Slakter JS, Yannuzzi LA, Schneider U, et al: Retinal choroidal anastomoses and occult choroidal neovascularization in age-related macular degeneration. *Ophthalmology* 107:742-53, discussion 753-4, 2000
  113. Slakter JS, Yannuzzi LA, Sorenson JA, et al: A pilot study of indocyanine green videoangiography-guided laser photocoagulation of occult choroidal neovascularization in age-related macular degeneration. *Arch Ophthalmol* 112: 465-72, 1994
  114. Spaide RF: Fundus autofluorescence and age-related macular degeneration. *Ophthalmology* 110:392-9, 2003
  115. Spaide RF, Hall L, Haas A, et al: Indocyanine green videoangiography of older patients with central serous chorioretinopathy. *Retina* 16:203-13, 1996
  116. Spaide RF, Yannuzzi LA: Manifestations and pathophysiology of serous detachment of the retinal pigment epithelium and retina, in Marmor MF, Wolfensberger TJ (eds): *The Retinal Pigment Epithelium*. New York, Oxford University Press, 1998, pp 439-55
  117. Starita C, Hussain AA, Patmore A, et al: Localization of the site of major resistance to fluid transport in Bruch's membrane. *Invest Ophthalmol Vis Sci* 38:762-7, 1997
  118. Suter M, Remé C, Grimm C, et al: Age-related macular degeneration. The lipofusion component N-retinyl-N-retinylidene ethanolamine detaches proapoptotic proteins from mitochondria and induces apoptosis in mammalian retinal pigment epithelial cells. *J Biol Chem* 275:39625-30, 2000
  119. Thompson JT: Retinal pigment epithelial tear after transpupillary thermotherapy for choroidal neovascularization. *Am J Ophthalmol* 131:662-4, 2001
  120. Toth CA, Pasquale AC, Graichen DF: Clinicopathologic correlation of spontaneous retinal pigment epithelial tears with choroidal neovascular membranes in age-related macular degeneration. *Ophthalmology* 102:272-7, 1995
  121. Verhoeff FH, Grossman HP: Pathogenesis of disciform degeneration of the macula. *Arch Ophthalmol* 18:561-85, 1937
  122. von Rückmann A, Fitzke FW, Bird AC: Fundus autofluorescence in age-related macular disease imaged with a laser scanning ophthalmoscope. *Invest Ophthalmol Vis Sci* 38: 478-86, 1997
  123. Voo I, Mavrofrides EC, Puliafito CA: Clinical applications of optical coherence tomography for the diagnosis and management of macular diseases. *Ophthalmol Clin North Am* 17:21-31, 2004
  124. Weinberger D, Lichter H, Goldenberg-Cohen N, et al: Retinal microangiopathies overlying pigment epithelial detachment in age-related macular degeneration. *Retina* 22:406-11, 2002
  125. Wolf S, Remky A, Elsner AE, et al: Indocyanine green video angiography in patients with age-related maculopathy-related retinal pigment epithelial detachments. *Ger J Ophthalmol* 3:224-7, 1994
  126. Yannuzzi LA: Retinal pigment epithelial detachment, in Yannuzzi LA (ed): *Laser Photocoagulation of the Macula*. Philadelphia, Lippincott, 1989, pp 49-63
  127. Yannuzzi LA: [Retinal pigment epithelial detachment]. *J Fr Ophthalmol* 12:761-74, 1989
  128. Yannuzzi LA, Hope-Ross M, Slakter JS, et al: Analysis of vascularized pigment epithelial detachments using indocyanine green videoangiography. *Retina* 14:99-113, 1994
  129. Yannuzzi LA, Slakter JS, Sorenson JA, et al: Digital indocyanine green videoangiography and choroidal neovascularization. *Retina* 12:191-223, 1992
  130. Yeo JH, Marcus S, Murphy RP: Retinal pigment epithelial tears. Patterns and prognosis. *Ophthalmology* 95:8-13, 1988
  131. Yoshida M, Abe T, Kano T, et al: Two types of optical coherence tomographic images of retinal pigment epithe-

- lial detachments with different prognosis. *Br J Ophthalmol* 86:737–9, 2002
132. Yoshitani S, Katsura M, Minamoto A, et al: Retinal pigment epithelial tear involving the fovea with preserved visual function. *Ophthalmic Surg Lasers Imaging* 34:217–20, 2003
  133. Yuzawa M, Kawamura A, Yamaguchi C, et al: Indocyanine green videoangiographic findings in detachment of the retinal pigment epithelium. *Ophthalmology* 102:622–9, 1995
  134. Zarbin MA: Current concepts in the pathogenesis of age-related macular degeneration. *Arch Ophthalmol* 122:598–614, 2004

---

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article. The authors thank Esther Eshkol for English language medical copyediting.

Reprint address: Shiri Zayit-Soudry, MD, Department of Ophthalmology, Tel-Aviv Sourasky Medical Center, 6 Weizmann St. Tel-Aviv 64239, Israel.

## Outline

- I. Introduction
- II. Pathogenesis
  - A. Pathophysiology of degenerative PED
  - B. Pathophysiology of drusenoid PED

- III. Clinical and angiographic features
  - A. Serous PED
  - B. Fibrovascular PED
  - C. Drusenoid PED
- IV. Optical coherence tomographic images
- V. Natural course
  - A. Serous PED
  - B. Fibrovascular PED
  - C. Drusenoid PED
- VI. Treatment options
  - A. Serous PED
  - B. Fibrovascular PED
  - C. Drusenoid PED
- VII. Summary
- VIII. Method of literature search