Graefe's Arch Clin Exp Ophthalmol
(2002) 240:533–538

CLINICAL INVESTIGATION

DOI 10.1007/s00417-002-0505-8

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Pigment epithelial detachment in the elderly

Clinical differentiation, natural course and pathogenetic implications

Received: 28 June 2001
Revised: 16 April 2002
Accepted: 8 May 2002
Published online: 25 June 2002

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Abstract *Background:* A prospective analysis was performed to characterize the angiographic appearance, natural course and prognosis of serous pigment epithelial detachments (PEDs) in elderly patients. The aim was to differentiate PEDs according to their angiographic characteristics and to analyze the specific clinical, visual and morphologic course of the different PEDs. *Methods:* Fluorescein and indocyanine green angiography were performed in 101 consecutive patients (53–87 years; 63 female, 38 male) with clinical signs of serous PED and drusen. *Results:* Different types of serous PED were identified: polypoidal choroidal vasculopathy (PCV)-associated PED in 14 patients (13.9%), vascular PED in 72 (71.2%), and avascular PED in 15 (14.9%). All PEDs resulted initially in similar visual loss. Avascular PEDs were smaller than vascular PEDs, and the latter were smaller than PCV-PEDs. During follow-up these differences were always present, but all PEDs enlarged initially followed by regression. This course was associated in all PEDs with progressive visual loss, accompanied by the development of RPE atrophy in avascular PEDs or disciform scars or RPE tears in the two other types. *Conclusion:* Despite different associations, all PEDs have a similar clinical course with respect to visual loss and enlargement or regression. This is compatible with the proposed common pathogenetic background with a hydrophobic barrier in Bruch's membrane causing fluid resulting from RPE pumping activity to accumulate between the pigment epithelium and Bruch's membrane.

Introduction

Serous pigment epithelial detachment (PED) in the elderly is a common manifestation of age-related macular degeneration (AMD) [5, 7, 13, 22, 30, 33]. Recently PED has been described as part of the spectrum of the clinical manifestation of polypoidal choroidal vasculopathy (PCV) [1, 21, 23, 25, 34, 35]. Whether or not the lesions occurring in these two settings have a common pathogenic background is in doubt.

The purpose of the present prospective longitudinal study was to subdivide serous PED in elderly patients according to their morphology by their fluorescein and ICG angiographic characteristics, and to correlate the findings with the visual and morphologic course of the disease and the proposed pathogenetic concepts of PED.

Patients and methods

Serous PED were analyzed and prospectively observed during follow-up in 101 consecutive patients with unilateral disease. Patients were included who were seen in our department because of recent visual loss due to a newly developed serous PED with associated drusen, with or without clinical evidence of associated CNV. The duration of visual loss had to be less than 3 months, but no limit as to the extent of visual loss was assigned. In all patients the fellow eye demonstrated signs of AMD, either early (67 pa-

tients) or late (34 patients). Patients were asked for written consent and the protocol of the study was approved by the local ethics committee.

The group consisted of 63 women (62.4%) and 38 men (37.6%). Their age was between 53 and 87 years (mean 70), and no other associated eye disease was present. The duration of follow-up was between 3 and 67 months (mean 10.7 months). The number of patients at each follow-up visit was comparable between the different PED groups, with 101 patients (100%) reviewed for 3 months, 80 (79.2%) for 6 months, 65 (64.4%) for 9 months, 48 (47.5%) 12 months, 40 (39.6%) for 15 months, 32 (31.7%) for 18 months and 10 (9.9%) for 24 months. At the initial examination and follow-up examinations every 3 months the following investigations were performed: ETDRS visual acuity, ophthalmoscopic fundus examination and fluorescein and indocyanine green (ICG) angiography. The area of PED was analyzed on the ICG angiogram, and the PED volume was measured using the Heidelberg Retina Tomograph (HRT Heidelberg, Germany) using a method resulting in reproducible volume measurements as demonstrated in earlier studies [27]. The total number of eyes with visual loss in each PED group was recorded, and the cumulative risk was analyzed using Kaplan–Meier statistics. In addition the distribution of other associated factors in the different groups was analyzed using chi-square statistics [2, 3]. A P value <0.05 was regarded as statistically significant. Because of the rapid diffusion of the dye into the serous PED, with fluorescein angiography an exact distinction of the PED and the type of the associated neovascular complex might be difficult. Because ICG demonstrates only minor diffusion into a PED the ICG angiograms were used to distinguish between vascular and avascular lesions as well as identifying the presence of PCV [30]. Subdivision of the lesions was undertaken as follows:

Type 1 PCV-associated PED (PCV-PED): PED associated with polypoidal choroidal vasculopathy.
Type 2 vascular serous PED: PED with angiographically visible choroidal neovascularisation (CNV).
Type 3 avascular serous PED: PED without evidence on fluorescein or ICG angiography of an associated neovascular complex. Because of the indistinct transition between larger confluent drusen and non-vascularized, drusenoid PED, these PEDs were defined as being >500 µm in diameter.

The initial visual acuity and the morphologic characteristics of the PED size and volume were recorded according to this classification. The natural course of the disease with relationship to the visual acuity, size and volume and morphologic development were documented.

Results

Initial characterization and differentiation of serous PED

The PED in the group of 101 patients were classified as follows:

Type 1 PCV-associated PED (PCV-PED): 14 patients (13.9%); mean follow-up 9.1 months
Type 2 Vascular serous PED: 72 patients (71.2%); mean follow-up 10.8 months
Type 3 Avascular serous PED: 15 patients (14.9%); mean follow-up 11.9 months

The period of follow-up in the different groups was similar (P=0.6) (Table 1) The mean initial visual acuity in all groups was 20/60, and the distribution in different groups of visual acuity was comparable (P=0.6) (Table 1). This was despite significant differences in the size (measured in mm^2) of the different types. The mean size of the PED was 13.9± mm^2 in PCV-PED, 9.8±5.4 mm^2 in vascular serous PED and 6.0±4.5 mm^2 in avascular serous PED (P<0.001).

The mean volume of the PED also differed among the three types: PCV-PED 3.53±1.8 mm^3, vascular serous PED 2.10±2.1 mm^3 and avascular serous PED 1.13±1.1 mm^3; P=0.005).

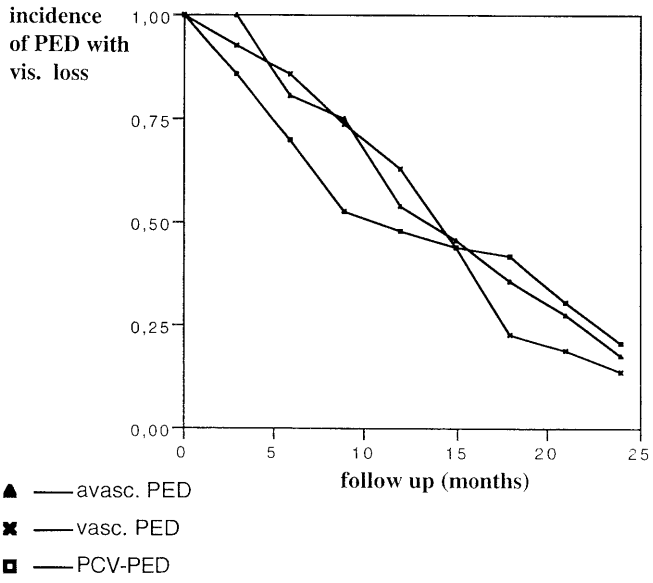

Fig. 1 Incidence of visual loss during follow-up (Kaplan–Meier analysis; P=0.9)

Table 1 Initial visual acuity in the different types of PED (P=0.6)

Visual acuity	Avascular PED	Vascular PED	PCV-PED
<20/200	1 (6.7%)	10 (13.9%)	0 (0%)
20/200–20/60	6 (40%)	30 (41.7%)	7 (50%)
>20/60	8 (53.3%)	32 (44.4%)	7 (50%)

Follow-up characterization of different PED

Loss of visual acuity (<3 lines) was observed during review in 55 patients (54.5%): 6 patients (40%) with avascular PED, 38 patients (52.8%) with vascular PED and 11 patients (78.6%) withPCV-PED (P=0.1). Also comparing the incidence of visual loss in relation to the duration of follow-up, no significant difference between the different types of PED could be seen (Fig. 1) (P=0.9). The mean final visual acuity was 1/18 in avascular PED, 1/24 in vascular PED and 1/30 in PCV-PED (P=0.1). The distribution of visual acuity also did not differ among the three groups (Table 2) (P=0.3).

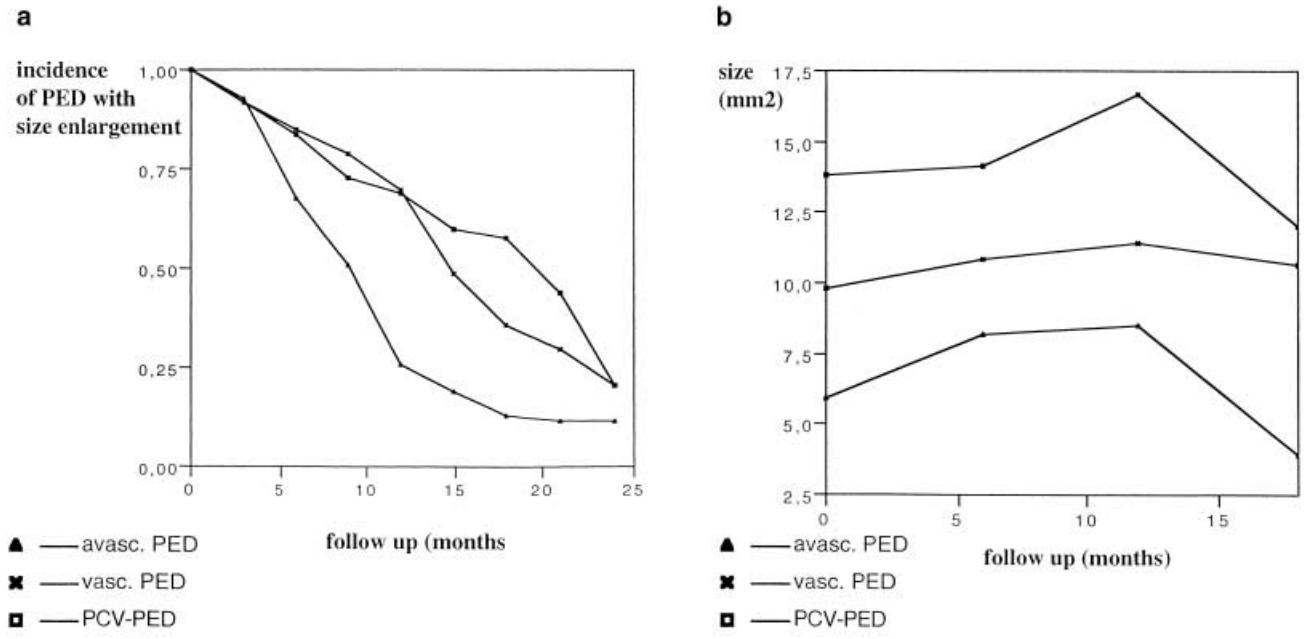

Fig. 2 **a** Incidence of enlargement in size during follow-up (Kaplan–Meier analysis; P=0.1). **b** Mean size initially and during follow-up (P<0.01)

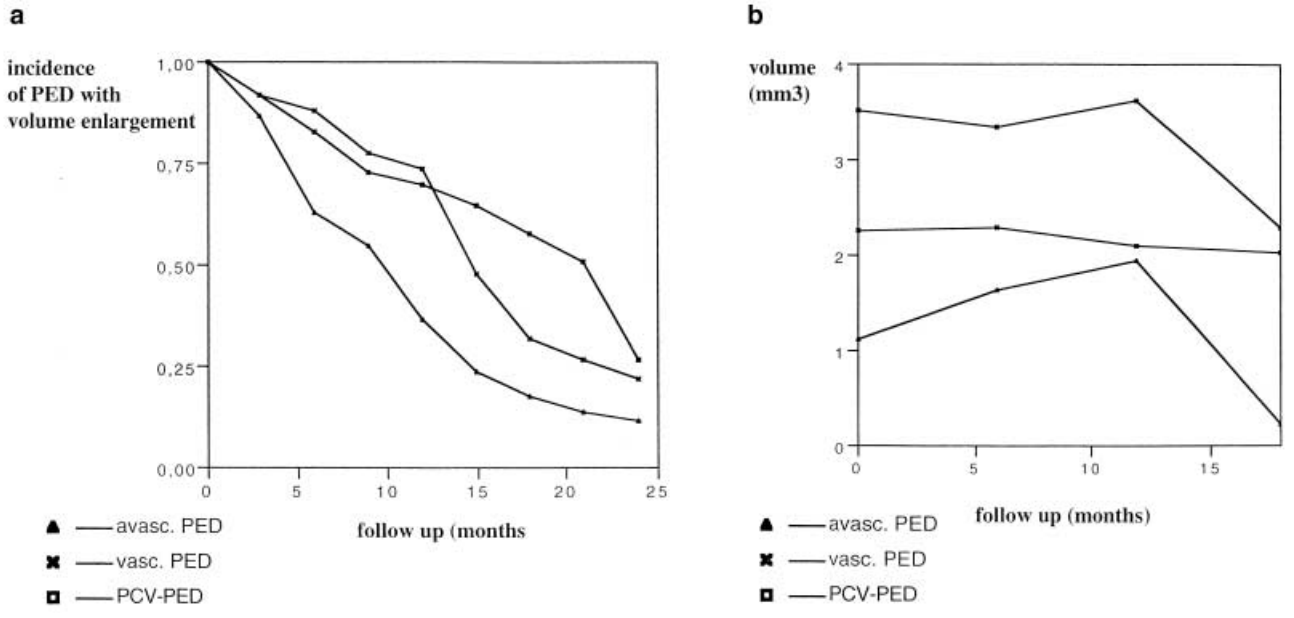

Fig. 3 **a** Incidence of enlargement in volume during follow (Kaplan–Meier analysis; P=0.06). **b** Mean volume initially and during follow-up (P<0.01)

Table 2 Final visual acuity in different types of PED (P=0.3)

Visual acuity	Avascular PED	Vascular PED	PCV-PED
<20/200	4 (26.7%)	28 (38.9%)	6 (42.9%)
20/200–20/60	5 (33.3%)	29 (40.3%)	7 (50%)
>20/60	6 (40%)	15 (20.8%)	1 (7.1%)

All three types demonstrated enlargement of the PED during the first months of follow-up, followed by a slight decrease in size. Increase in diameter developed similarly in all groups and was observed in 10 avascular PEDs (66.7%), 32 vascular PEDs (44.4%) and 4 PCV-PEDs (28.6%) (P=0.1). The time course of the incidence of enlargement also did not differ among the three groups (Fig. 2a) (P=0.1). However, these very similar developments occurred on three different levels, with avascular PEDs being the smallest, vascular PEDs intermediate in size and PCV-PEDs the

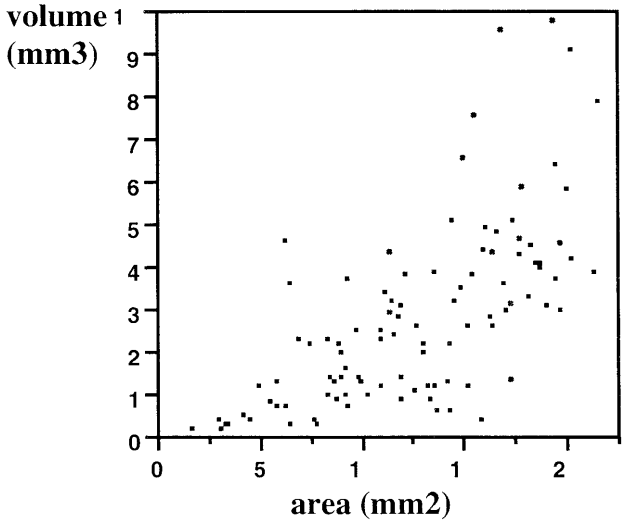

Fig. 4 Maximal size and volume initially of PED which developed a RPE tear (×) or not (■) during follow-up

Table 3 Morphologic development of serous PED during follow-up (P=0.3)

Findings	Avascular PED	Vascular PED	PCV-PED	all PED
Persistent PED	8 (53.3%)	38 (52.8%)	5 (35.7%)	54 (53.4%)
RPE atrophy	5 (33.3%)	8 (11.1%)	1 (7.1%)	11 (10.9%)
Disciform scar	1 (6.7%)	17 (23.6%)	6 (42.9%)	24 (23.8%)
RPE tear	1 (6.7%)	9 (12.5%)	2 (14.3%)	12 (11.9%)

largest; the difference between the three groups ws always significant (Fig. 2b) (P<0.01). A similar course was seen concerning the volume of the PED. An enlargement in volume was observed in 10 avascular PEDs (66.7%), 32 vascular PEDs (44.4%) and 5 PCV-PEDs (35.7%) (P=0.1). The time course of enlargement did not differ among the three groups (Fig. 3a) (P=0.1). Throughout the evolution avascular PEDs had the smallest diameter and volume, vascular PEDs were intermediate and PCV-PEDs were the largest. The differences among the three groups were always significant (Figs. 2b, 3b) (P<0.01).

The morphologic changes associated with the change in size and volume, and the cause of the progressive visual loss were predominantly the development of geographic atrophy in avascular PED and of RPE tears or disciform scars in vascular PED and PCV-PED (Table 3). RPE tears only developed in PEDs with large size and volume (Fig. 4).

Discussion

In agreement with other studies [1, 4, 7, 8, 9, 12, 13, 15, 20, 22, 23, 25, 30, 32, 33, 34, 35] we have found that PEDs can occur under different circumstances. However, all three types of PED were qualitatively similar in their behavior in that the initial visual acuity and visual deterioration during review were comparable. In addition all three types followed were alike in the course of the disease, with enlargement in size and volume over several months and later regression associated with either RPE atrophy, disciform scarring or RPE tears (Fig. 5).

However, some quantitative differences were apparent. PCV-PEDs were initially larger with less tendency to further enlargement in area or volume [1, 23, 31, 34, 35]. A majority developed hypertrophic subretinal scarring. This is in contrast to reports of spontaneous resolution in this type of PED [1, 33, 35], but these studies included PCV-PED in younger patients as well as individuals of non-Caucasian origin.

Vascular PEDs were the most common category in the present study. They were initially medium sized, but area and volume of the PED enlarged with eventual regression. This resulted most often in a disciform scar, but as found in other studies [27] RPE tears sometimes developed. In general RPE tears most often developed in initial large PED and increased further in volume, resulting in sufficient tangential stress to rupture the RPE [8, 9, 24].

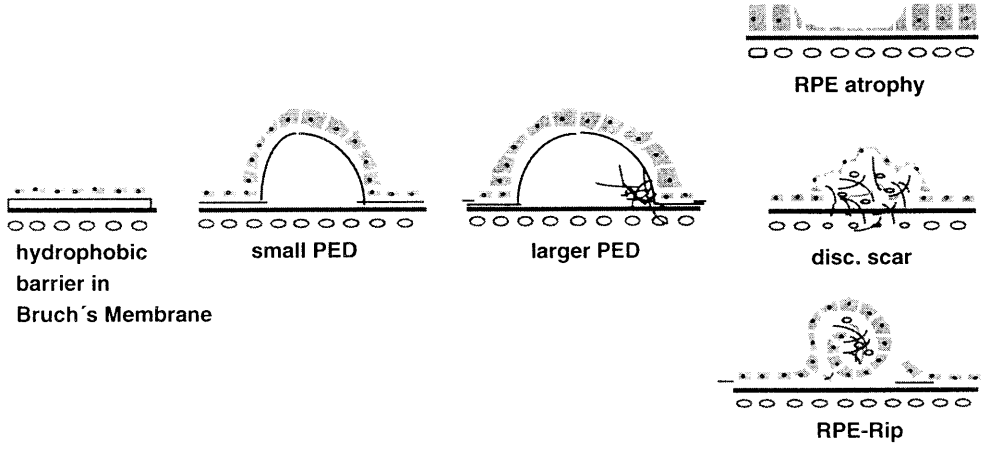

Fig. 5 Schematic summary of the development and course of different serous PED entities

Avascular PEDs as demonstrated by ICG and fluorescein angiography were initially smaller. Despite their small size their effect on visual acuity was comparable to that of the other two types of PED. They also enlarged during follow-up but remained relatively small and finally regressed. After several months of follow-up there was progressive visual loss, most commonly associated with RPE atrophy, although the final vision was somewhat better than in the other two types of PED. The small number of avascular PEDs that grew to the size of the other forms all developed evidence of new vessels during the study.

It has been hypothesized that detachment of the RPE is consequent upon the presence of a hydrophobic barrier to the outward passage of fluid at the level of Bruch's membrane, due to accumulation of neutral lipids. There is strong circumstantial evidence to support this hypothesis [6, 10, 11, 14, 17, 18, 19, 26, 28, 29], but this pathogenetic concept has never been shown to correlate with the natural course of different clinical PED entities. The similar clinical behavior of the different lesions during follow-up implies that this mechanism may be common to all three. The source of fluid may represent the only difference among them, and may explain the quantitative differences. In the avascular lesions the fluid is believed to accumulate from the outward movement of ions and material by the RPE. In vascular lesions the new vessel complex would contribute to the accumulation (Fig. 5). Therefore, it was hypothesized that the hydrophobic barrier in Bruch's membrane is responsible for the fluid accumulation under the RPE, but another factor in Bruch's membrane, the RPE or the retina is responsible for development of choroidal neovascularization under the RPE ("dual pathogenetic pathway"). This may result in specific therapeutic approaches in the different types of PED.

The situation in PCV is less clear. In one histologic study it has been reported that the vascular complex is internal to Bruch's membrane [16]. If this is the case the venous complex would contribute to the fluid. There is a clinical impression that in some cases the complex is within the choroid, and both situations may exist. In the latter case, serous detachment of the retinal pigment epithelium may not occur, but the lesion would present with hemorrhage or retinal edema. This difference in anatomic site may account for the spontaneous resolution of some lesions.

In conclusion, the natural course of the different clinical entities of PED supports the concept that a specific significant hydrophobic barrier in Bruch's membrane is central to the pathogenesis of the lesion whether or not there are new vessels of PCV.

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