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Retinal Pigment Epithelial Detachment and Choroidal Neovascularization in Senile Disciform Macular Degeneration

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Senile disciform macular degeneration is classified into two groups: the pigment epithelial detachment (PED) group and the non-pigment epithelial detachment group. It is not clear whether choroidal neovascularization occurs in the PED group, although it has been shown that choroidal neovascularization takes place in the latter group. The purpose of the present study is to investigate the relationship between PED and choroidal neovascularization, visual prognosis, and the probability of photocoagulation for PED in senile disciform macular degeneration.

Our retrospective study consists of 29 consecutive untreated patients (30 eyes) over 50 years of age all having PEDs except for one patient. The results are as follows:

1. Detachment was defined as serous (S-PED) in 9 eyes, combined (C-PED) in 12 eyes, and hemorrhagic (H-PED) in 9 eyes.

2. Detachment larger than 5 disc diameters was discovered in 1 of the 9 eyes (11.1%) in S-PED, none in the 12 eyes (0%) in C-PED, and 3 of the 9 eyes (33.3%) in H-PED.

3. Incidence of the notch sign was observed in 56% of S-PED, 67% in C-PED, and 89% in H-PED. In proportion to the extent of hemorrhage in the PED, incidence of the notch sign was increased. Abnormal hyperfluorescence was detected quite close to PED in all the patients under fluorescein angiography.

4. We classified the abnormal hyperfluorescence including the notch sign into three types based on the angiograms: patch-, tuft-, and reticular. These types were nearly always found to have subpigment epithelial neovascularization. The shape was different from those of pigment epithelial detachment (PED), and early irregular filling and late slight leakage of the dye were different from those of pigment epithelial detachment (PED) and atrophy of the retinal pigment epithelium (RPE).

5. Prognosis for visual acuity was rather good. However, it is highly possible that we can directly treat choroidal neovascularization in a notch, which is not covered with subpigment epithelial blood, before neovascular membrane reaches the center of the foveal avascular zone. Although a large number of PED were involved in the fovea at the time of the intial visit.

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Key words: Senile macular degeneration, Pigment epithelial detachment (PED), Choroidal neovascularization, Notch sign, Fluorescein angiography

1 Introduction

Senile disciform macular degeneration (SDMD) continues to grow as the world's population gets older and one of the most important causes of legal blindness is SDMD[1-2]. SDMD is characterized by the presence of a choroidal neovascularization and/or pigment epithelial detachment (PED). Gregor and Joffe[3] reported that there was a much greater prevalence of disciform macular degeneration in Caucasians (3.5%) than in black Africans (0.1%). We have already reported the natural history of idiopathic

choroidal neovascularization, and suggested that Japanese differ from Caucasians in respect to the incidence of bilaterality, and visual prognosis[4]. The present report describes a study of 30 eyes with hemorrhagic or serous detachment of the retinal pigment epithelium (RPE). The purpose of this study is to investigate the relationship of PED regarding the chorodial neovascular membrane, including the notch sign, visual prognosis, and the necessity of photocoagulation therapy for PED.

2 Material and Methods

We undertook a retrospective study of 29 consecutive untreated patients (30 eyes) over the age of 50 years with PEDs, who were referred to the Department of Ophthalmology at Sapporo Medical College from 1980 to 1986, with the exception of one patient, aged 39.

The criteria for the diagnosis of a PED was established as the local elevation of the RPE with halo and pooling of fluorescein dye or blocked fluorescence due to blood or serous exudate in the subpigment epithelial space in angiography.

The following detail were recorded: the age and sex of the patients, duration of symptoms, corrected visual acuity, the size, location, and ophthalmoscopic features of the PEDs, together with the pattern of fluorescence in fluorescein angiography. Patients with serous retinal pigment epithelial detachment associated with severe myopia, angioid streaks, choroidal tumors and idiopathic central serous choroidopathy were not included in this study.

In the first part of the study, detachments were grouped into three categories: serous (S-PED), combined (C-PED), and hemorrhagic (H-PED). S-PED (Fig. 1-a) was characterized by a clear subpigment epitheliel fluid without blood in the subpigment epithelial space. Fluorescein angiography showed hyperfluorescence spread diffusely beneath the entire detachment in the early phase, and the dye pooled into the subpigment epithelial space with well demarcated margins. H-PED (Fig. 1-c) was defined by the presence of a total bleeding in the subpigment epithelial space, which corresponded with blocked hypofluorescence as discovered in fluorescein angiography. Combined group (Fig. 1-b) was characterized by partial bleeding in the subpigment epithelial space, and showed a demarcation line between fluid and blood.

The size of PED was recorded by measuring the average of the largest horizontal and vertical diameters of the detachment in the disc diameters (DD). Notch sign (Fig. 2-a to 2-c) was defined by a flattening or an indentation of the margin of PED.

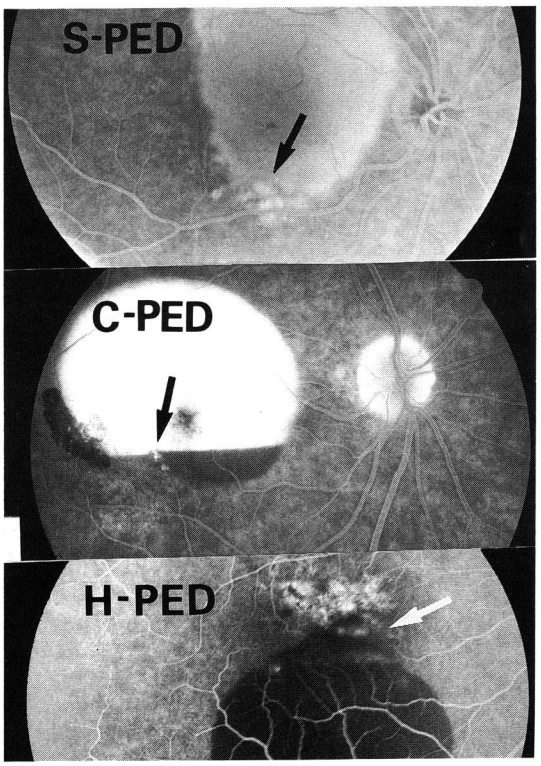

Fig. 1 Classification of pigment epithelial detachment with a notch (an arrow).
Top: Serous pigment epithelial detachment (S-PED)
Middle: Combined pigment epithelial detachment (C-PED)
Bottom: Hemorrhagic pigment epithelial detachment (H-PED)

3 Results

3·1 PED and choroidal neovascularization

Of the 29 patients, 20 were male and 9 female. The age range at the first outpatient visit was 38 to 78 years with the median being 65.6 years.

Detachment was found in 9 eyes in S-PED, 12 eyes in C-PED and 9 eyes in H-PED (Table 1). Detachment diameter at the initial visit was found to be from 0.8 to 5.0 DD with the average being 2.6 DD. A size comparison of the detachment in each group is shown in Table 2. The large PEDs of more than 5 DD in the serous group was 1 out of 9 eyes (11.1%), none of the 12 eyes in the combined group, and 3 of 9 eyes in the hemorrhagic group (33.3%). The initial PED involving the foveal avascular zone was 22 of the 30 eyes (73.3%), and not involving was 8 (26.7%). Bilateral PEDs were observed in only one patient, whose one eye had already shown PED at the time of the first visit and the other eye developed PED during the follow-up period. The incidence of the notched PED was 70.0%. Notch sign was found in 55.6% of the serous group, 66.7% in the combined group, and 88.9% in the hemorrhagic group (Table 2).

Abnormal hyperfluorescence which included the notch sign was detected around the PED in all cases. We classified the hyperfluorescent spots into three types based on the angiograms: patch-, tuft-, and reticular (Fig. 3). The patch-type was characterized by a disseminated patchy hyperfluorescence. Fluorescein angiogram of the tuft- or the reticular-type showed tuft or reticular subretinal hyperfluorescence which is caused by a fluorescent dye filling the capillaries of the choroidal neovascular membrane in the early phase. These hyperfluorescent spots rarely showed any leakage of the dye during the early phase, but tissue stainning was distinct during the late phase in all the types.

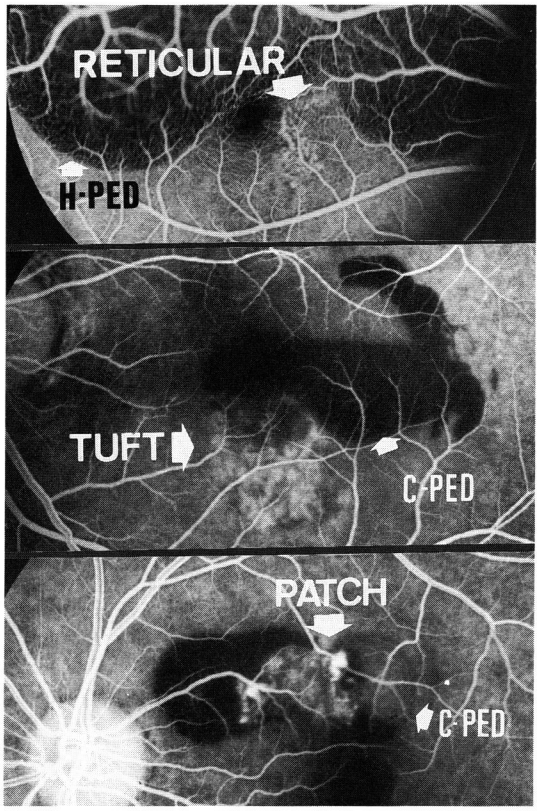

Fig. 2 Pattern of abnormal hyperfluorescence based on fluorescein angiography.
Top: Reticular (Vascular) pattern (a large arrow).
Middle: Tuft-like (Vascular) pattern (a large arrow).
Bottom: patch-like pattern (a large arrow). Small arrows showing PED of various types.

In eyes with serous PED, 89% were of the patch-type, but in the eyes of the combined group 50% were of the tuft-type, 42% were of the patch-type, in eyes of the hemorrhagic group 56% were of the patch-type, 22% were of the tuft-type, and 22% were of the reticular-type (Table 2).

In the intial findings, subretinal hemorrhages were found in 22% of the 9 eyes in the serous group, whereas 58% was found in the combined group and 56% in the hemorrhagic group.

The site of abnormal hyperfluorescence was found to be in the para-foveal (more than 200 μ from the center of foveal avascular zone) in 20 eyes (67%), the juxta-foveal (less than 200 μ) in 5 eyes (17%), and the sub-foveal in 5 eyes (17%). Localization of abnormal hyperfluorescence was in contact with detachment of RPE in 25 of the 30 eyes (83%).

Table 1 *Classification of pigment epithlial detachment*

Classification	No.	(%)
S-PED group	9	(30.0)
C-PED group	12	(40.0)
H-PED group	9	(30.0)
Total	20	(100.0)

3·2 Clinical course of PED

Of the 21 eyes followed for more than 3 months, enlargement of PED was discovered in 9 eyes. Develop-

Table 2 *Initial examination data for 30 eyes with PED*

	Group of PED			
	S-PED n=9 (%)	C-PED n=12 (%)	H-PED n=9 (%)	Total n=30 (%)
Size of PED				
less than 1DD	3 (33.3)	4 (33.3)	4 (44.4)	11 (36.7)
1-4DD	5 (55.6)	8 (66.7)	2 (22.2)	15 (50.0)
5DD or more	1 (11.1)	0 (0)	3 (33.3)	4 (13.3)
Notch sign				
present	5 (55.6)	8 (66.7)	8 (88.9)	21 (70.0)
absent	4 (44.4)	4 (33.3)	1 (11.1)	9 (30.0)
Subretinal hemorrhage				
present	2 (22.2)	7 (58.3)	5 (55.6)	14 (46.7)
absent	7 (77.8)	5 (41.7)	4 (44.4)	16 (53.3)
Pattern of abnormal hyperfluorescence				
Patchy	8 (88.9)	5 (41.7)	5 (55.6)	18 (60.0)
tuft	1 (11.1)	6 (50.0)	2 (22.2)	9 (30.0)
reticular	0 (0)	1 (8.3)	2 (22.2)	3 (10.0)

ment of subretinal neovascularization was observed in 4 eyes, expansion of abnormal hyperfluorescence was noted in 4 eyes, increased bleeding in the detachment of the RPE, and the appearance of subretinal bleeding was observed in 2 eyes, respectively. Development of serous PED after the absorbance of bleeding under RPE was seen in 3 eyes in the hemorrhagic group (Total number of lesions was 26.) (Table 3).

Four eyes were treated by a xenon, argon, or krypton laser photocoagulation. Two eyes in the combined group were treated by confluent photocoagulation of the choroidal neovascular membrane. The visual acuities improved during the study period. One eye in this combined group having many scattered burns on the surface of the PED developed a new choroidal neovascular membrane, thereafter. Visual acuity deteriorated to 0.05. One patient with foveal hemorrhagic detachment who finally gained good visual acuity (1.0), underwent photocoagulation on the subpigment epithelial neovascular membrane after absorption of the subpigment epithelial hemorrhage.

3·3 Visual prognosis of patients with PED

Of the 21 eyes which were observed for 3 months or more (The follow-up period ranged from 3 to 66 months with an average of 26.2 months) final visual acuity of 0.5 or more was observed in 13 eyes (61.9%), from 0.1 to 0.4 for 3 eyes (14.3%), from 0.01 to 0.09 for 3 eyes (14.3%), and counting finger for 2 eyes (9.5%) (Table 4). Visual acuity declined more than two lines in 7 eyes (33.3%) and improved in 8 eyes (38.1%), and no change in vision was observed in 6 eyes (28.6%) (Table 5).

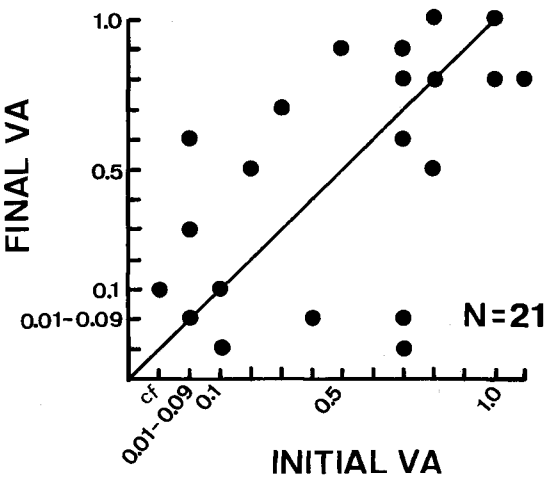

Fig. 3 Relationship between initial and final visual acuity.

Table 3 *Summary of chorioretinal lesion changes in 21 eyes followed up for 3 months or more. (The total number of lesions)*

Lesions	S-PED n=3*	C-PED n=10*	H-PED n=8*
Developed subretinal neovascularization	1	1	2
Enlargement of hyperfluorescence	2	0	2
Enlargement of the PED	1	5	3
More bleeding in the PED	1	1	0
Subretinal hemorrhage	0	1	1
Development of serous PED	/	/	3
Photocoagulation	0	3	1

(* " n " : total number of eyes)

Table 4 *Final visual acuity*

Visual acuity	No.	(%)
counting finger	2	9.5
0.01-0.09	3	14.3
0.1-0.4	3	14.3
0.5 or better	13	61.9

Table 5 *Changes of visual acuity between the first examination and completion of the study*

Visual acuity	No.	(%)
Better	8	38.1
Same	6	28.6
Worse	7	33.3

4 Discussion

4·1 Pigment epithelial detachment

There were differences in the visual prgnosis, incidence of choroidal neovascularization, and the effectiveness of various laser photocoagulations between the two groups of SDMD : the PED group and the non-PED group[5].

Detachment of the RPE was defined as well demarcated, and dome-shaped elevations of the RPE. In fluorescein angiography, S-PED revealed early filling and late pooling of the dye beneath the RPE, and H-PED showed a block of the choroidal background fluorescence owing to the hemorrhage under the RPE. It is possible that S-PED switched to the C- or H-PED as a result of later bleeding beneath the RPE.

4·2 Notch sign and occult choroidal neovascularization in PED

Notched PEDs were seen in 21 of the 30 eyes (70.0%) in the present study. The notch sign was found in 55.6% of the 9 eyes of the serous group, in 66.7% of the 12 eyes of the combined group, and in 88.9% of 9 eyes of the hemorrhagic group. The percentage of S-PED with a notch was almost the same as the Gass's study (38 of the 55 eyes, 69.1%)[6].

Yoshioka and Oojima[7] reported that the notch sign had no relation to be the development of S-PED because the notch was apart from it. However the abnormal hyperfluorescences including the notch sign were detected to have contact with PED in most of the patients in our study.

We believe that the notch sign is the most important sign of choroidal neovascularization in PED. The noth of the RPE is supposed to be induced by the tight adhesion of the RPE to the Bruch's membrane. It is strongly suggested that existance of the neovascular membrane in the notch when it is accompanied with one or more of the other signs such as hot spots, lipid, fluid levels within the PED[6]. C-PED and H-PED are reported to have choroidal neovascularizatoin, because their bleeding beneath the RPE was a sign of occult neovascularization. Gass[6] has already reported that 92% of the 35 eyes with the notch developed one

or more additional signs of chorodial neovascularization during a follow-up study of 5 months or more in S-PED.

According to Gass, the blood flow within the neovascular network may increase and the exudation and extravasation of erythrocytes may start. If endothelial decompensation is confined primarily to one portion of the network, it may cause a serous detachment of the adjacent RPE. In such cases, a notched, or reniform-shape pigment epithelial detachment develops around the margin of the neovascular network.

Similar notching may occur at the edge of an occult neovascular membrane in H-PED. The combined group of PED is induced by sudden bleeding under the S-PED, which is caused by the occult sub-pigment epithelial neovascular membrane.

A higher incidence of the notch sign was present in the combined group (66.7%), or the hemorrhagic group (88.9%) than in the serous group (55.6%). These findings were similar to those reported by Poliner *et al.*[8]

We classified the hyperfluorescent spots including the notch sign into three groups. It is not always easy to make a definite distinction among them. Characteristics of the three groups as shown by angiography display a varied degree of dye fillings with tissue staining which is characteristic of the choroidal neovascular membrane beneath the RPE[7]. Hyperfluorescences such as tuft- and reticular- types are considered to be caused by choroidal neovascularization due to the vascular pattern and dye staining in the later phase of angiography[9]. However it is not always certain that hyperfluorescences of the patchy-type were choroidal neovascularization or not, because of the smallness of the lesions under RPE.

Yoshioka[10] reported on the likelihood that the primary lesion in macular subretinal neovascularization will appear in the focal area of hyperpigmentation after the acute retinal pigment epitheliitis and will develop new vessels beneath the RPE. Though none of the eyes had clinically definite evidence of neovascular membranes during the initial visit, they often went on to develop neovascularization[5]. As regards this phenomenon, Sarks[11], and Green and Key[12] have shown that the choroidal neovascularization associated with gaps in the Bruch's membrane was found more often histologically than it was recognized clinically. It was shown that blood vessels at this level might not always involve detached RPE and did not necessarily cause a loss of visual acuity[13].

Sometimes, the choroidal neovascular membrane from fibrovascular ingrowth through a break in the RPE may cause serous or hemorrhagic PED. Abnormal hyperfluorescence including the notch sign was in contact with PED in all our patients. This shows a close relationship between choroidal neovascularization and S-PED as well as C-PED and H-PED. However a definite cause-and-effect relation between choroidal neovascularization and PED was not established in the present study.

4·3 Visual prognosis

The prognosis was excellent in the group of patients whose ages were 55 years or younger with extrafoveal detachment of the RPE of one disc diameter or less. In most of these patients development of a neovascular membrane was not seen[5,13-15]. In a report on the patient with S-PED, Elman *et al.*[5] showed that although a large number of eyes were able to maintain functional visual acuity, 25% of the eyes had severe and irreversible visual loss usually due to complications of choroidal neovascularization. In 140 eyes which developed choroidal neovascular membranes, 32% of them were associated with a final visual acuity of 20/200 or worse. However in our study, ages of the patients were 50 or older with the exception of one case. PEDs were larger than 0.8 DD with an average of 2.6 DD and involved the foveal avascular zone in 73.3% of the 30 eyes. Of the 21 eyes observed for 3 months or more, final visual acuities of 0.5 or more were found in 13 eyes (61.9%), and worse than 0.1 were discovered in 5 eyes (23.8%). A large number of eyes (66.7%) were able to maintain initial visual acuity at the completion of our study, whereas a final visual acuity of 0.1 or worse was reported as 61.6% in the Poliner *et al.* study[8]. The visual prognosis was

fairly good in our patients. Casswell *et al.*[13] showed similar results in S-PED, but not in the case of the non-PED group of SDMD[4,16-21]. The reasons for this discrepancy between the PED group and the non-PED group were speculated as follows:

1) Choroidal neovascular membrane may be limited to the subpigment epithelial space with the intact RPE and neuroepithelium[12] in the PED group. In contrast, the membrane in the non-PED group has grown through both the Bruch's membrane and RPE damaging the photoreceptor.

2) The choroidal neovascularization in the PED group can be detected earlier than in the non-PED group because of a visual loss secondary to PED, before the choroidal neovascularization involves the fovea.

4·4 Photocoagulation for PED

In senile disciform macular degeneration, the PED group may differ form the non-PED group in the response to photocoagulation as well as the natural history. The Macular Photocoagulation Study (MPS) demonstrated that the argon laser photocoagulation to choroidal neovascular membranes outside the foveal avascular zone in the non-PED group improved the visual prognosis when compared with the natural course[20,22]. However there is no evidence to suggest that photocoagulation at any wavelength (argon, ruby, krypton, and argon dye lasers) to various types of PED is either beneficial or safe at present[23]. Bird[24], using an argon laser and xenon photocoagulation, reported flattening in 21 of the 24 S-PEDs. Schatz and Patz[25] showed similar results in 71 eyes with S- or H-PEDs. However the Moorefields Macular Study Group[26] reported that argon laser photocoagulation is not beneficial for SDMD with S-PED.

In the past the method of photocoagulation for PED[23-25] consisted of a grid pattern, a C-shaped pattern, and non-contiguous burns straddling the margin of the S-PED without a definite detection of the neovascular membrane instead of the present use of direct coagulation for choroidal neovascularization. Although PED involved the foveal avascular zone in 73.3% of the cases at the initial visit, a choroidal noevascularization still remained in the extra-foveal area in our study. Therefore, it is possible to photocoagulate the choroidal noeovascular membrane early enough before the membrane has the opportunity to invade the fovea. In H-PED with a notch, it is highly possible that we can directly treat choroidal neovascularization with a notch which is not covered with subpigment epithelial blood.

The criteria for the selection of patients in consideration of photocoagulation at the present time should fulfill the following two items;

1) PEDs which have a sign of choroidal neovascularization, involvement of fovea and visual loss.

2) The distance which is 200 μ or more from the foveal edge of the choroidal neovascularization to the center of the foveal avascular zone.

In addition, the need for randomized controlled studies to document the role of photocoagulation for choroidal neovascularization combined with PED must be emphasized.

5 Conclusions

We undertook a retrospective study of 29 consecutive untreated patients (30 eyes). They were 50 years or older with pigment epithelial detatchments (PEDs) with the exception of one patient.

1) Detachment was defined as serous (S-PED) in 9 eyes, combined (C-PED) in 12 eyes, and hemorrhagic (H-PED) in 9 eyes.

2) Detachment larger than 5 disc diameters was observed in 1 eye (11.1%) in the serous group, none (0%) in the combined group, and 3 eyes (33.3%) in the hemorrhagic group.

3) Incidence of the notch sign was 56% in the serous group, 67% in the combined group, and 89% in the hemorrhagic group. In proportion to the extent of the bleeding in the PED, an incidence of the notch sign was increased. There were abnormal hyperfluorescence with tissue staining of the dye around PED, which was not accompanied by a notch sign.

4) We classified abnormal hyperfluorescences with or without the notches into three types based on the angiograms: patch-, tuft-, and reticular. These cases were nearly always found to have subpigment epithelial neovascularization.

5) Of the 21 eyes followed for three months or more, visual acuities of 0.5 or more were observed in 61.9%. Visual acuity which improved more than two lines were 38.1%, and no change in vision was observed in 28.6%.

In conclusion, abnormal hyperfluorescence including the notch sign appears to be an indication of choroidal neovascularization. It is detectable easily in the early stage when the new vessel is limited under the RPE and does not reach the foveal avascular zone. Therefore it is possibile to photocoagulate for the PED of SDMD.

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老人性円盤状黄斑部変性症における網膜色素上皮剝離と脈絡膜新生血管

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老人性円盤状黄斑部変性症（SDMD）には網膜色素上皮剝離で始まるものと色素上皮剝離を起さず，漿液性網膜剝離や網膜下出血で始まるものとがある．後者については脈絡膜新生血管の関与が明らかとなっている．しかし前者は同じ病気でありながら，症例も少なく，脈絡膜新生血管との関係が必ずしも明白とはいえない．今回，色素上皮剝離を呈する病型にたいし，Gassの報告したnotch signを中心に網膜色素上皮剝離と脈絡膜新生血管との関係，自然経過，および光凝固治療の可能性について検討した．

対象症例は1例を除き，50歳以上であった．これらの症例を網膜色素上皮剝離の性状から，漿液性群9眼，出血性群9眼，および混合性群（漿液性剝離に出血が合併するもの）12眼に分類した．

色素上皮剝離の大きさは0.8から5.0乳頭径大で平均2.6乳頭径であった．漿液性群，混合性群より出血性群のほうに色素上皮剝離の大きいものが多く認められた．

また初診時に脈絡膜新生血管の徴候である網膜下出血の合併率は出血性群55.6%，混合性群58.3%に対し，漿液性群は22.2%と低い傾向が見られた．

notch signは色素上皮剝離の内部に食い込むように陥凹を示した．蛍光造影では通常の色素上皮剝離に見られる一様な蛍光流入像と異なり，不規則でやや強い過蛍光が認められた．notch signの頻度も出血性群88.9%，混合性群66.7%，漿液性群55.6%と色素上皮剝離内の出血の程度に応じてnotch signの合併頻度が高くなる傾向が認められた．色素上皮剝離の近辺にはnotch signおよびそれ以外の異常過蛍光像が蛍光造影にて全例に検出された．

これらnotch signを含めた異常過蛍光線の性状を分類すると不規則斑状，房状，および網目状の3型に分類された．蛍光造影では造影初期に強い過蛍光を呈するが，造影後期には軽い蛍光の漏出および組織染色となる．したがってこれらの異常過蛍光は網膜色素上皮の萎縮を示す背景蛍光の増強（window defect）ではなく，脈絡膜新生血管と推定された．notch sign以外の異常過蛍光像は色素上皮剝離と大部分が隣接していた．

位置的に色素上皮剝離は73.3%が中心窩無血管帯を含むが，脈絡膜新生血管を示唆する異常過蛍光（notch signを含む）は中心窩から離れて，光凝固の可能なpara-fovealが20眼67%を占めた．

最終視力は0.5以上が62%で，初診時と比べ2段階以上の改善38.1%，不変28.6%，悪化が33.3%であり，視力予後は色素上皮剝離を呈しない症例に比べそれほど不良ではなかった．

以上のことからSDMDに見られる網膜色素上皮剝離の視力予後は色素上皮剝離を呈しないものと比べ比較的良好である．蛍光造影所見からnotch signと他の異常過蛍光像は脈絡膜血管新生の徴候であり，網膜色素上皮剝離の原因と推定された．また色素上皮剝離の症例は脈絡膜新生血管が中心窩無血管帯に達しない早期に発見できるので，光凝固治療の可能性が示唆される．