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Stabilization of visual acuity with photodynamic therapy in eyes with chorioretinal anastomoses

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Abstract *Purpose:* (1) To evaluate, in a non-randomized, institutional, prospective study, the efficacy of photodynamic therapy with Visudyne (PDT) in neovascular age-related macular degeneration (AMD) eyes with chorioretinal anastomoses (CRA). (2) To review, in a retrospective study and for comparison, the natural evolution of neovascular AMD eyes with CRA. *Methods:* Prospective clinical and angiographic study of 17 consecutive eyes with CRA, treated with PDT. Retrospective clinical and angiographic study of the natural course of 17 consecutive patients with CRA. Masked best-corrected visual acuity (VA) and angiographic features at baseline and during the period of one year were evaluated. *Results:* The two groups presented similar characteristics at baseline regarding age, sex, initial VA, duration of follow-up and angiographic features. PDT-treated eyes showed, at 1-year follow-up, VA stabilization or improvement in 73.3% of the eyes, no cases with very severe VA loss, and no fluorescein leakage in 46.6% of the eyes. In contrast, at 1-year follow-up the natural evolution of CRA was characterized by severe or very severe VA loss in 69% of the eyes and statistically significant mean VA loss (P=0.001) with persistence of fluorescein leakage in all cases. *Conclusion:* The natural history of AMD eyes with CRA leads to progressive and dramatic VA loss, which is associated with blindness in most of the cases. PDT with verteporfin can offer some benefit to these patients, allowing VA stabilization or improvement in more than two thirds of the cases, at one year.

Introduction

Chorioretinal anastomoses (CRA), in eyes with age-related macular degeneration (AMD), have been associated with different designations, such as deep retinal vascular anomalous complex or retinal angiomatous proliferation [1, 2, 3, 4, 7, 10]. Cases of CRA are considered to make up as much as 10–15% of the newly diagnosed cases of neovascular age-related macular degeneration (AMD). Differentiation of this particular form of AMD has not been carried out in most clinical trials on AMD. No proven treatment exists to date [7, 10].

Clinicopathological [4], clinical and angiographic features suggesting the presence of CRA [7] have been extensively described. More recently, different stages of evolution were proposed [10]. We have chosen, for our studies, the characterization of these lesions proposed by Slakter [7] (Table 1).

Natural evolution is thought to be associated, in almost every case, with significant decrease in visual acui-

Table 1 Criteria for characterization of CRA: biomicroscopy, photographic and angiographic features suggesting the presence of CRA in exudative AMD eyes

Biomicroscopy and stereo red-free photography	FA and ICG
Intra or preretinal hemorrhages or retinal edema	Leakage at retinal level
Dilated retinal vessels	√
Retinal–retinal anastomosis	√
Ring of lipid exudates and PED	√
Sudden termination of dilated and/or tortuous "going-down" retinal vessel	√
	FA and/or ICG hot spots (not due to PE atrophy)
	Chorioretinal anastomoses
	Two-tier angiographic complex[6] on ICG

ty, fibrosis and atrophy. Indocyanine-green-guided laser photocoagulation (ICG-guided laser) of the "hot spots" has shown poor results in these eyes [3]. Recently, a number of oral reports have suggested that photodynamic therapy (PDT) with Visudyne may be of value for the treatment of CRA, but no prospective studies have been published.

The purpose of this study was: (1) to evaluate, in a non-randomized, institutional, prospective study, the efficacy of PDT with Visudyne in neovascular AMD eyes with CRA; (2) to review the natural evolution of neovascular AMD eyes with CRA in a retrospective comparative study.

Patients and methods

A prospective institutional study was performed in 17 consecutive patients, observed after January 2000, with exudative AMD and CRA who were treated with PDT with Visudyne. PDT treatments were performed within 3-month intervals, using the standard protocol of VIP (verteporfin in PDT) and TAP (treatment of AMD with PDT) trials [8, 9]. Retreatments were applied if fluorescein angiography showed any leakage from the neovascular lesion, causing VA decrease.

A retrospective comparative study was carried out, for comparison, in 17 consecutive patients with neovascular AMD and CRA.

All patients in both series were older than 50 years of age at the time of diagnosis and presented signs of AMD. Only patients with 6 or more months of follow-up were considered for the studies.

The criteria for diagnosis of CRA were based on Slakter's [7] descriptions and are summarized in Table 1. We considered the possibility that biomicroscopic and red-free findings suggested the presence of CRA when intraretinal or preretinal small hemorrhages and intraretinal edema (cystoid or not) were associated with two or more additional features (Table 1). Fluorescein angiography (FA) and indocyanine-green video-angiography (ICG) were highly suggestive of CRA when early and/or late focal "hot spots" were present and associated with one or more additional findings (Table 1). Definitive CRA was assumed only when positive signs were identified on biomicroscopy and red-free photography and with at least one of the two photographic techniques. Lesions were ≤5400 μm in size (greatest linear dimension) in all cases at the time of diagnosis.

Cases with disciform scars in the study eye or with other fundus diseases associated with choroidal neovascularization (CNV), such as angioid streaks, juxtafoveal telangiectasias type 2, myopia, trauma and intraocular infection or inflammation, were excluded in both prospective and retrospective studies.

Stereo color and red-free fundus photographs and stereo fluorescein and digital ICG angiograms obtained with the Topcon Image Net system were reviewed in all cases in the two series by two independent reviewers (R.M.S., J.R.F.A.) and any disagreement was resolved by a third reviewer (J.G.C.V.).

In both series, VA was tested by a masked observer using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart; the best-corrected VA was obtained in all patients. The evolution of VA was classified in three groups: 1- VA improvement (moderate: <3 lines, and significant: ≥ 3 and ≤ 6 lines); VA stabilization (VA change ≤ to 1 line); and VA decrease (moderate: <3 lines, severe: ≥3<6 lines, and very severe: ≥6 lines).

Student's *t*-test (differences between means) and MedCalc (comparison of proportions for percentages) were used for statistical analysis.

No significant differences between the two groups were found at baseline in age (P=0.4, Student's *t*-test), sex (P=0.3, Student's *t*-test), initial VA (P=0.19, Student's *t*-test), follow-up period (P=0.4, Student's *t*-test) or angiographic features (Tables 2, 3 and 4).

Table 2 Results of prospective and retrospective studies at 1 year. (P difference between initial VA and VA at 3, 6 and 12 months)

	n	Age (years)	VA				VA improvement		VA stabilization (%)	VA loss		
			Initial	At 3 months	At 6 months	At 12 months	≤6≥3 lines (%)	<3 lines (%)		Moderate (%)	Severe (%)	Very severe (%)
Natural evolution, 1 year	13	74.5	20/105	20/245	20/311	20/329	0	0	7.6	30.7	30.7	38.3
				P=0.01	P=0.003	P=0.001						
Prospective study (PDT), 1 year	15	74.6	20/149	20/169	20/149	20/137	20	0	53.3	20	20	0
				P=0.3	P=0.4	P=0.4						

Table 3 Results of PDT treatment in AMD eyes with CRA (*NLP* no light perception)

Patient	Age (years)/ sex	Follow-up (months)	VA change (lines)			Initial VA	VA of other eye	Number of treatments	Leakage at last observation
			At 3 months	At 6 months	At 12 months				
1	78/F	12	–9	–9	–5	20/32	20/160	3	No
2	71/M	6	–1	–1	–	20/40	20/25	3	Yes
3	79/F	15	0	0	0	20/200	20/800	4	Yes
4	77/F	12	0	0	0	20/200	20/800	1	No
5	77/M	21	1	–1	–2	20/40	20/63	1	No
6	75/M	12	0	–1	–1	20/40	20/40	3	No
7	75/M	6	1	1	–	20/200	20/25	3	Yes
8	50/M	12	0	0	0	20/50	20/20	5	Yes
9	86/F	12	0	0	0	20/200	20/800	4	No
10	78/F	24	–1	–4	–3	20/25	20/640	7	Yes
11	72/F	12	–4	–5	–4	20/100	20/800	5	Yes
12	76/F	18	0	3	3	20/800	20/800	3	No
13	71/F	24	0	3	3	20/80	20/800	8	Yes
14	78/F	15	0	0	0	20/200	20/1600	2	No
15	76/F	12	0	0	0	20/50	NLP	4	Yes
16	76/F	18	0	1	3	20/200	20/800	6	No
17	74/F	30	0	–1	–1	20/80	20/800	8	Yes

Table 4 Natural evolution of AMD eyes with CRA

Patient	Age (years)/ sex	Follow-up (months)	VA change (lines)			Initial VA	VA of other eye
			At 3 months	At 6 months	At 12 months		
1	81/M	12	–3	–3	–3	20/200	20/160
2	70/F	6	–3	–7	–	20/25	20/800
3	78/F	15	0	0	–1	20/160	20/160
4	81/M	12	–10	–10	–10	20/80	20/25
5	69/F	24	–1	0	–2	20/25	20/800
6	77/F	12	0	0	–3	20/400	20/40
7	75/M	6	0	0	–	20/200	20/25
8	85/F	12	–3	–4	–4	20/80	20/800
9	60/F	9	–0	–1	–	20/25	20/20
10	80/F	24	–12	–12	–8	20/32	20/800
11	75/M	12	–3	–3	–7	20/80	20/800
12	77/F	18	–3	–15	–7	20/40	20/400
13	74/F	30	–4	–4	–7	20/100	20/500
14	81/M	15	–3	–6	–5	20/200	20/25
15	77/M	6	–4	–4	–	20/63	20/25
16	56/F	36	0	0	–2	20/40	20/500
17	72/F	30	–1	–1	–2	20/50	20/800

Results

Prospective study: photodynamic therapy

Seventeen eyes of 17 patients, 11 women and 6 men, with an average age of 74.64 years (range 50–86) were treated with PDT with Visudyne. Mean follow-up period was 15.3 months (range 6–36) and mean number of PDT sessions was four (range one to eight).

All the patients were observed at 3 and 6 months. Fifteen patients were observed at 1 year follow-up. The mean initial VA was 20/149 (20/800–20/25) and the mean final VA was 20/141 (20/320–20/50). The difference between initial VA and VA at 1 year was not statistically significant (P=0.4, Student's t-test) (Tables 2, 3, 4), indicating stabilization. The ICG hot spots were extrafoveal in 88.2% of the eyes at initial observation.

VA stabilization or improvement was present in 88.2% and 82.4% of the eyes at 3 and 6 months, respectively. Severe or very severe VA loss had occurred in 11.8% and 17.6% of the eyes at 3 and 6 months respectively. Fifteen patients were observed at 12 months. Stabilization or improvement of VA was found in 73.3% of the eyes and severe VA loss had occurred in 20% of the

eyes. VA improvement was present in 11.8% of the eyes at 6 months and in 20% at 12 months (Table 2).

No foveal exudation was present at 1 year in 46.6% of the eyes and no PDT was performed at that time. Two eyes presented recurrence of exudation after two or more consecutive observations with no FA leakage and no PDT treatment and 12 or more months of follow-up (cases 3, 17).

In 64.7% of the patients, the VA of the contralateral eye was ≤20/200 (Table 3). Disciform scars with retinal chorioretinal anastomoses were present in all of them. One of the contralateral eyes also had a central retinal artery occlusion. Pigment epithelium detachment (PED) documented with FA and ICG was present in 64.7% of the eyes at the time of diagnosis.

No PED rip or preretinal, intraretinal or subretinal extensive hemorrhages occurred in the treated eyes.

Retrospective study: natural evolution

A retrospective study of the natural evolution of 17 consecutive eyes with AMD and CRA was performed on 17 patients, 11 women and 6 men, with an average age of 74.5 years (range 56–85) and a mean follow-up period of 16 months (range 6–36), beginning at the time of diagnosis. All the patients were observed at 3 and 6 months, and 13 patients were observed at 1 year. An extrafoveal hot spot on ICG was predominant (82.3%) at the time of diagnosis.

VA stabilization or improvement occurred in 58.8% of the eyes and severe or very severe VA loss occurred in 41.2% at 3 and 6 months. At 1 year, VA stabilization was present in only 7.6% of the eyes and severe or very severe VA loss had occurred in 69% of the eyes. The contralateral eye of 52.9% of the patients, presented, at the time of enrolment, a VA of ≤20/400 and disciform scars with retinal choroidal anastomoses (Table 4).

At 3 and 6 months, there was no significant difference in the proportion of eyes with visual loss in both series, but at 12 months, the proportion of eyes with visual loss was 26.7% in the PDT group vs 92.3% in the natural history group (P=0.003).

Discussion

Our study evaluates the efficacy of PDT in AMD eyes with CRA compared with the natural course of the disease. We have found that PDT stabilizes VA in eyes with CRA until one year of follow-up, offering, therefore, a better alternative. As far as we know, no previous reports have been published on this subject.

CRA, a subcategory of exudative AMD is a relatively well defined entity. The diagnosis of CRA can be suspected by an expert physician, using only biomicroscopy and red-free photography. For this study, we used well-defined objective criteria (Table 1). FA and particularly ICG were used for confirmation of the diagnosis. A definitive diagnosis of CRA was only performed when positive features were present on biomicroscopy, red-free photography and at least one of the two different angiograms, FA and ICG.

Our study has one important limitation, namely that it is based on a comparison between prospective and retrospective analyses. However, the similarity between the two groups regarding age, sex, initial VA, follow-up period, and angiographic features reduces the confounding factors that may have influenced the outcome (Tables 3 and 4).

Females, who are generally more affected than males [7, 10], represented, in our series, 64.7% of the patients of the PDT and natural evolution groups. The marked tendency to severity, bilateral and symmetry of manifestations of the disease [7, 10] was also present in the two series (Tables 3 and 4). 64.7% and 52.9% of the patients of the PDT and natural evolution, respectively, presented manifestations of the disease in the contralateral eye associated with a VA ≤20/200.

The natural evolution group showed, at 12 months, VA stabilization in 7.6% of the eyes and VA loss in 92.3%. The VA decrease was severe or very severe in 69.2%. No eyes had VA improvement and in 76.9% VA was ≤20/200 at 1 year. The poor outcome of the natural evolution group was already expected at the 3-month follow-up, when 58.8% of the eyes presented severe or very severe VA decrease (compared with only 11.7% of the PDT group eyes at the same duration of follow-up). At the end of the follow-up the mean VA decrease of the natural evolution group was statistically significant (P=0.002); 70.5% of the eyes were legally blind and all the eyes presented subfoveal leakage of fluorescein. Therefore, the natural course of CRA eyes appears to be characterized by severe or very severe VA loss in the first 3–6 months in nearly half of the eyes as in our series (Fig. 1). Additional VA loss occurs in the following months, with at least two thirds of the eyes becoming legally blind, with no treatment, in a mean period of 16.4 months. Leakage on FA persists for months or years and the initial lesion is progressively being replaced by fibrous tissue. The most common end stage is a disciform scar with multiple retinal choroidal anastomoses.

Eyes with CRA that we treated with PDT showed better results than those that followed the natural course. At 1 year, the PDT-treated eyes showed VA stabilization or improvement in 73.3% of the eyes and absence of subfoveal fluorescein leakage in 46.6% of the eyes. The best VA results, compared with natural evolution, were seen at 3 months (only 11.7% of the eyes with severe or very severe VA loss) and at 6 months (17.6% of the eyes with severe or very severe VA loss). After a mean follow-up of 15.3 months, no eyes experienced very severe VA loss, with 35.3% of the eyes maintaining final VA of

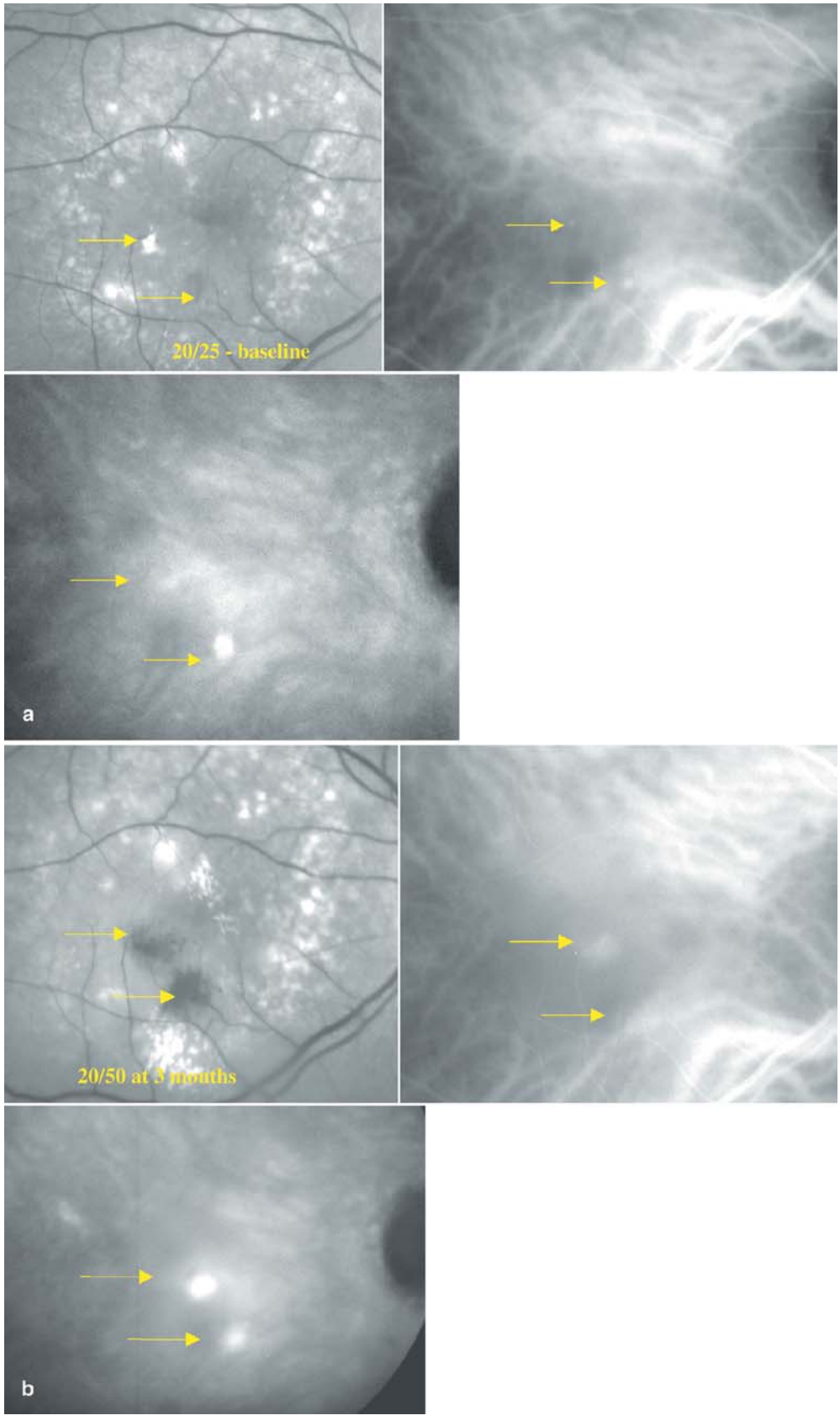

Fig. 1a, b Natural evolution of CRA: case 2. **a** Baseline images. Intraretinal hemorrhages and hard exudates on red-free images and two hot spots on early and late ICG are visible. VA is 20/25. **b** Three months later VA is 20/50, a ring of lipid exudation is visible, intraretinal hemorrhages are bigger, and ICG shows two hot spots and PED

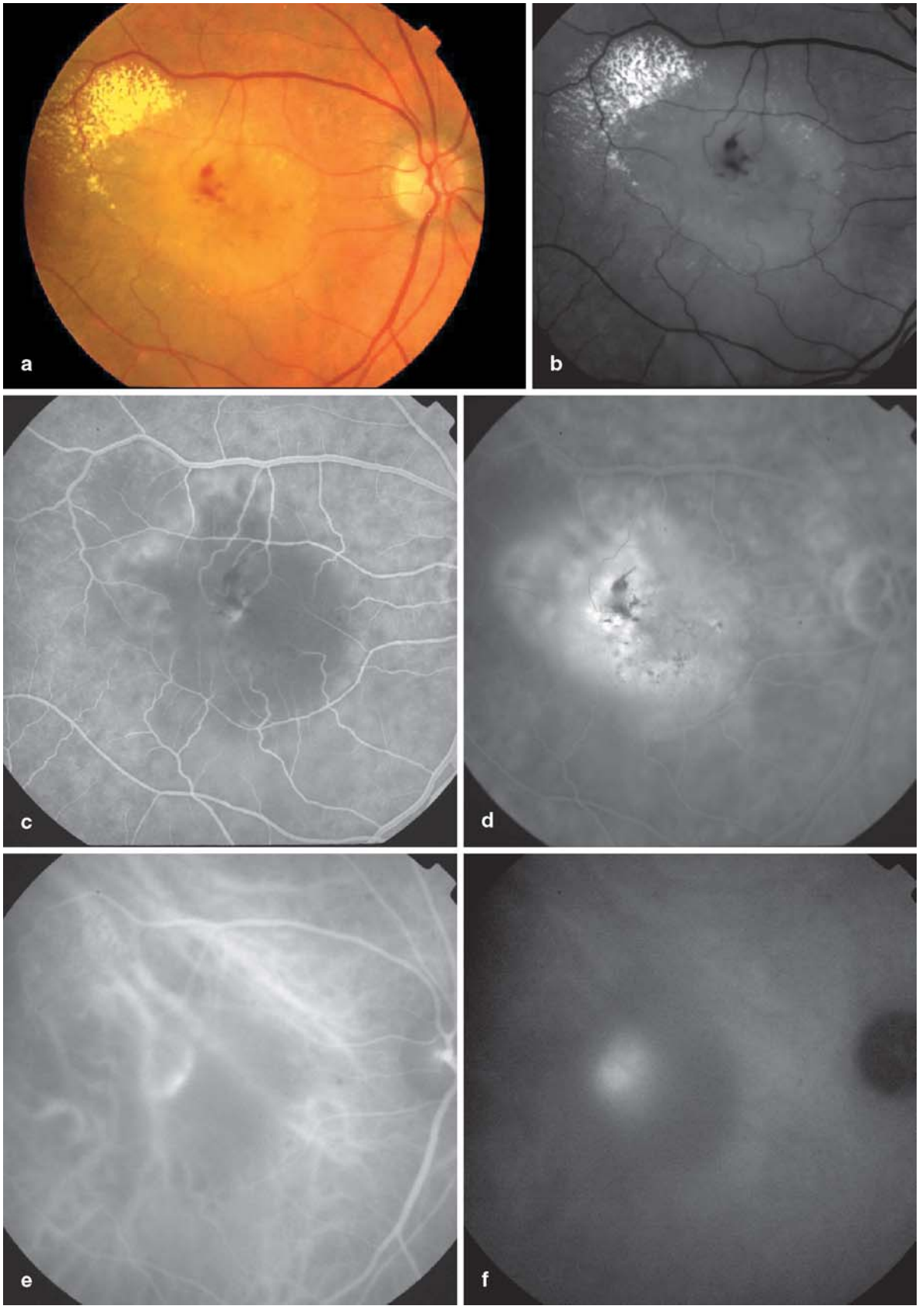

Fig. 2a–f Legend see page 374

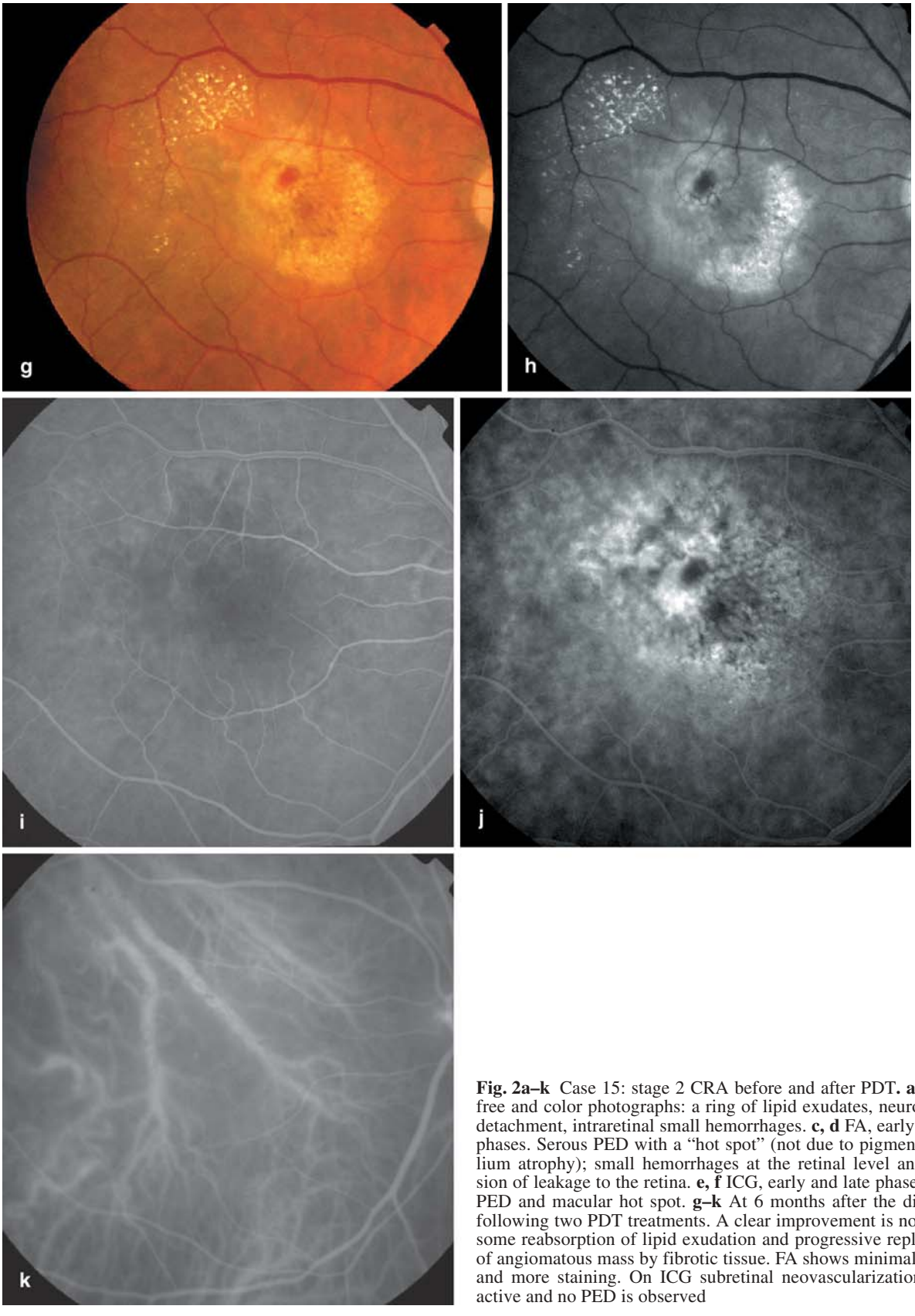

Fig. 2a–k Case 15: stage 2 CRA before and after PDT**. a, b** Red-free and color photographs: a ring of lipid exudates, neurosensory detachment, intraretinal small hemorrhages. **c, d** FA, early and late phases. Serous PED with a "hot spot" (not due to pigment epithelium atrophy); small hemorrhages at the retinal level and extension of leakage to the retina. **e, f** ICG, early and late phases. Large PED and macular hot spot. **g–k** At 6 months after the diagnosis, following two PDT treatments. A clear improvement is noted with some reabsorption of lipid exudation and progressive replacement of angiomatous mass by fibrotic tissue. FA shows minimal leakage and more staining. On ICG subretinal neovascularization is less active and no PED is observed

≥20/63; 70.5% of the eyes showing VA stabilization or improvement, and no leakage being present in 47% of the eyes at the final observation.

The selection of the spot size for PDT may be a controversial issue. The ICG hot spot would probably indicate the size of the lesion. ICG and verteporfin share some properties; they have the same molecular weight and the same affinity to bind with proteins. It could be speculated that verteporfin will stain only what ICG stains, because of the similar characteristics of the two substances. However, similar leaking and staining properties of both ICG and verteporfin have not yet been confirmed. No pooling of ICG occurs in serous PED, and probably no pooling of verteporfin will occur either. It has therefore been proposed that the spot size for PDT should be the same size as that of the hyperfluorescence seen on ICG. However, we have chosen to treat the lesion with the size visualized on FA (largest diameter plus 1 mm) because there is no experience of ICG-guided PDT, and verteporfin has not yet been successfully imaged with good specific resolution in humans [6]. Our decision is also based on our experience in treating hot spots with laser photocoagulation. In many treated cases, the ICG control at 2–3 weeks showed hyperfluorescence at the border of the scar after the laser photocoagulation. At the beginning, this was assumed to be caused by the persistence of the neovascularization. With retreatment, a new hyperfluorescence was visible. The digital overlay showed that all the initial lesions had been treated during the first and second treatment. We may speculate that with laser photocoagulation, some flattening of PED may occur near the scar and partial visualization of CNV is possible. One of these patients was later submitted to surgery and a CNV with the same size as the PED was excised. The masking effect of the serous PED probably prevented the visualization of CNV on ICG.

During follow-up, some of the treated eyes developed a classic CNV component. The role of PDT in this evolution cannot be ruled out. However, identical behavior has been described in natural evolution of subfoveal CNV [5, 6, 8, 9]. In our series, PDT achieved a progressive closure of this classic CNV component.

Some arguments have been put forward suggesting that eyes with CRA should not be treated with PDT. One reason is the possibility of intraretinal ICG leakage in some CRA eyes and an expected similar behavior with verteporfin. Neurosensory damage would occur with PDT. Another reason is related to the possibility of PED rip with PDT. In most of the cases, the intraretinal or subretinal leakage documented on ICG is extrafoveal or juxtafoveal. PDT can be useful in these cases, before progression of the lesion to the subfoveal space. This benefit may be greater than the potential neurosensory damage. PED rips have also been described to occur as a result of PDT or laser photocoagulation [5]. No cases of PED rip developed in our series.

PDT-treated eyes showed a variable response to the treatment. In some eyes, after the first or second treatment, the ICG hot spot became larger, a classic component of the lesion became apparent or bigger on FA, and VA decreased. Over time, leakage decreased on FA, serous PED became flatter, the ICG hot spot became attenuated or disappeared, and the lesion became progressively atrophic and/or fibrotic. An extrafoveal scar progressively developed with stabilization of VA (Fig. 2). Eyes with larger PED seemed to be associated with a worse prognosis. In other eyes (e.g., cases 3, 17), recurrence occurred after a period of 6 months or more without treatment. In these eyes ICG hot spot was present during the whole follow-up, even in the absence of fluorescein leakage. The importance of this feature is difficult to evaluate due to the small number of cases and the persistence of plaque or focal hyperfluorescence in eyes showing no recurrences.

In conclusion, AMD eyes with CRA showed a natural course towards very severe VA loss and blindness. Our study suggests that PDT with verteporfin can offer some benefit to AMD eyes with CRA, allowing VA stabilization or improvement in more than two thirds of the eyes, and absence of leakage in nearly half of the eyes at one year. Larger prospective studies and identification of CRA eyes in randomized clinical trials will certainly offer new insights into the treatment of this particular form of AMD.

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