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Is there any relationship between photodynamic therapy for exudative age-related macular degeneration and choroidal neovascolarization recurrence? A rationale for combined treatments

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PURPOSE. *Photodynamic therapy (PDT) is the treatment of choice for subfoveal choroidal neovascularization (CNV) in age-related macular degeneration (ARMD). Interpretation of PDT mechanism of action is not yet fully understood and causes of CNV recurrences are unclear. The authors have conducted a retrospective analysis of fluorescein and indocyanine green angiographies in patients treated with multiple PDT in order to identify risk factors for recurrence.*

METHODS. *A total of 342 eyes of 342 patients (207 women and 135 men) with ARMD and subfoveal CNV were treated with at least two PDT. Angiographic (fluorescein and indocyanine green) features of recurrences were confronted to pretreatment examinations in all patients.*

RESULTS. *Post-PDT angiographies showed in all eyes a dark circle corresponding to the laser spot even 1 year after treatment. Persistence or progressive regrowth of CNV developed in an area adjacent or corresponding to the original lesion, without any specific relationship with the location of fluorescein and indocyanine green late leakage or with presence of abnormal fluorescence due to pigment abnormalities. At the 3-month angiographic follow-up, 23 patients (6.7%) showed a recurrent CNV resembling shape and dimension of the laser spot used for the PDT treatment.*

CONCLUSIONS. *The authors failed to identify angiographic signs helpful to predict the risk of CNV persistence or recurrence. PDT leaves minor but persistent changes in the choroidal vasculature within the treatment area. In some cases, the recurrent CNV seems to be related to the laser spot of the PDT. (Eur J Ophthalmol 2006; 16: 686-94)*

KEY WORDS. *Age-related macular degeneration, Choroidal neovascularization, Choroidal neovascularization recurrence, Photodynamic*

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INTRODUCTION

Age-related changes of the retina may progressively lead to visual impairment mainly due to photoreceptor loss in the posterior pole. Visual symptoms remain limited until choroidal new vessels (CNV) become evident. As CNV break through the Bruch membrane, visual function suddenly deteriorates, for exudative and hemorrhagic changes which take place in the macular area. As it is well known, though atrophic age-related macular degeneration (ARMD) is far more frequent, the wet form is responsible for most cases of ARMD-related blindness (1-3).

These considerations justify all the efforts to find a strategy to treat the exudative form by closing the CNV or

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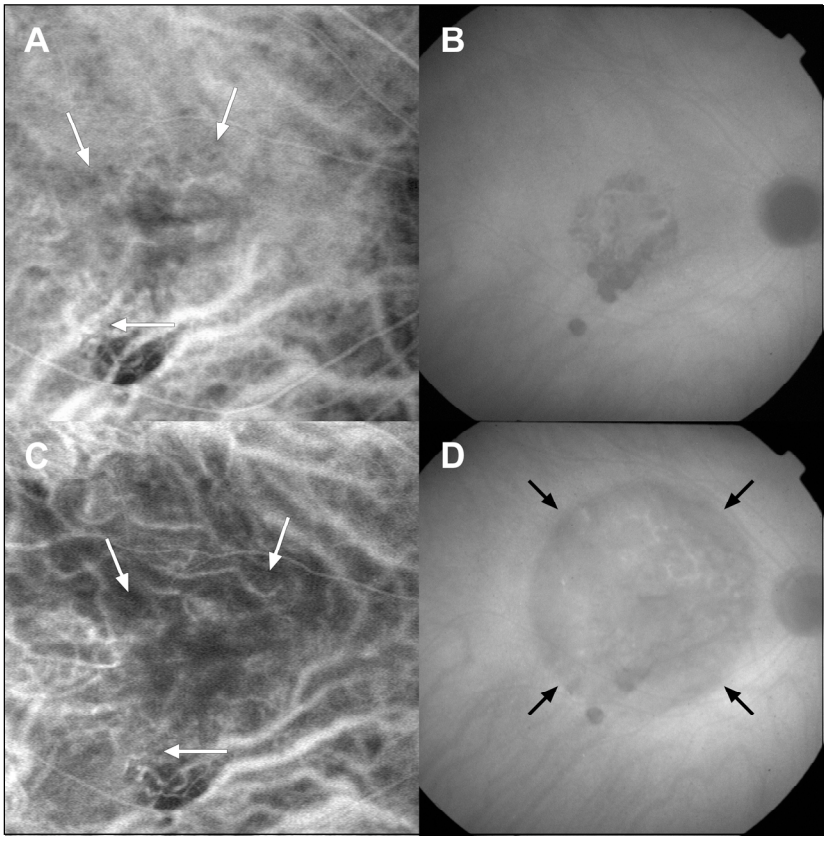

Fig. 1 - *Pre-photodynamic therapy (PDT) indocyanine green (ICG) angiography shows the barely visible choroidal neovascularization surrounded by normal choroidal vasculature* (**A**)*; in the late phases a significant leakage of dye is visible at the posterior pole* (**B**)*. Three months after PDT, within the area of the laser spot a rarefaction of the choroidal vasculature is evident with disappearance or modification of some choroidal vessels (white arrows in* **A** *and* **C**)*. In the late phases the same area shows less fluorescence than the surrounding choroid (black arrows)* (**D**)*.*

limiting their growth and proliferation. Despite good results reported by MPS study with laser photocoagulation, these data can only be applied to extrafoveal CNV that, however, represent the minority of CNV. Most CNV extend and proliferate beneath the fovea, thus a direct photothermal coagulation cannot be performed without critical consequences on foveal structures (4-7).

The rationale of PDT is based on the possibility of producing a photothrombosis within the targeted vessels that have been previously labeled by a photosensitizer (verteporfin). This leads to a temporary closure of the CNV. Despite a frequent but partial recanalization or regrowth of the new vessels, multiple treatments induce a progressive reduction of the leakage from the choroidal membrane, which is currently clinically considered an inactivation of a potentially harmful lesion. This procedure has led to significant clinical results in preserving/ameliorating visual function not only in exudative ARMD but also in pathologic myopia and other CNV-associated diseases (8-14).

After a 5-year experience with PDT, it has been clarified that one of its major drawbacks is the need for multiple treatments. In order to understand if some angiographic features could help to predict a greater risk for CNV recurrences or persistences, we have retrospectively analyzed the angiographies of 342 patients with ARMD-related CNV, who have been treated with multiple PDT, according to TAP criteria. Also, as more patients undergo PDT treatments, some unusual effects of the procedure are more frequently observed. We present here clinical evidence of a correspondence between shape/dimension of some recurrent/persistent CNV and the laser spot that had been used for the previous PDT procedure.

PATIENTS AND METHODS

This retrospective study included 342 eyes of 342 patients (207 women and 135 men) with ARMD and predominantly classic or occult CNV (226 and 116 eyes, respectively). Mean GLD before any PDT was 3.1 mm (SD=2.3 mm). All patients had been treated with at least two sessions of PDT (mean number of sessions = 4.1±2.4), according to the TAP protocol criteria, between January 2001 and December 2003, at the Department of Ophthalmology of the University of Padova. Mean follow-

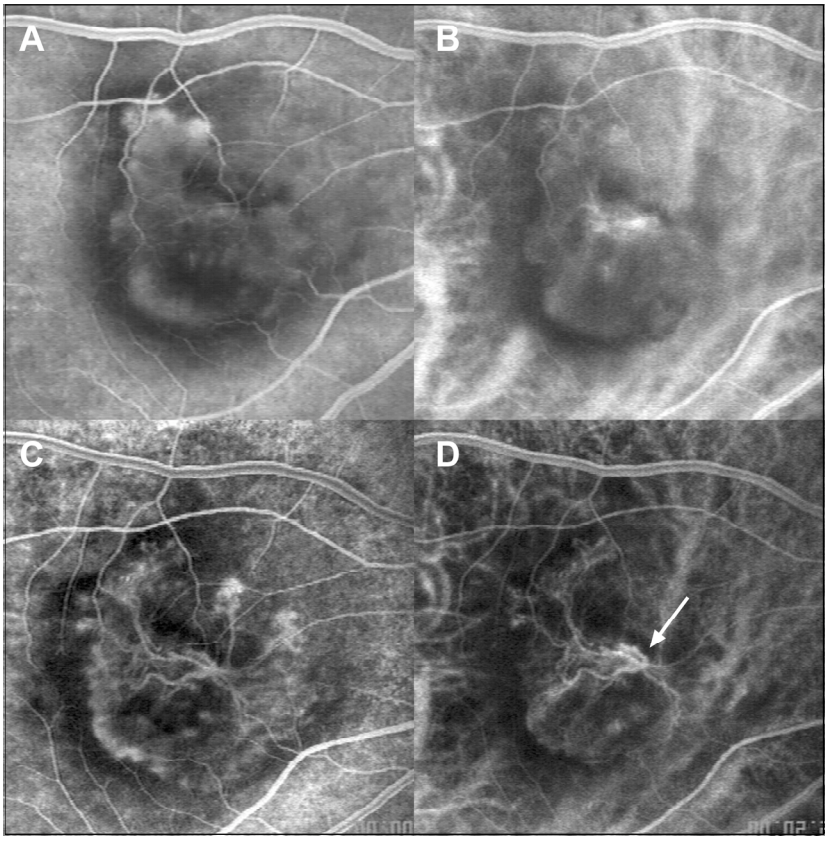

Fig. 2 - *In the pre-photodynamic therapy (PDT) fluorescein and indocyanine green (ICG) angiography (***A** *and* **B***, respectively), despite the presence of a well-delineated classic neovascularization, a feeder vessel is not visible. In the same eyes, 3 months after PDT, when a recurrence is evident, a feeder vessel (arrow) can more easily be distinguished both in fluorescein (***C***) and ICG (***D***).*

up was 26±9 months. Demographic data are shown in Table I.

Static and dynamic fluorescein and indocyanine green (ICG) angiographies (Topcon Imagenet 50IA, Tokyo, Japan; SLO Rodenstock, München, Germany, respectively) were performed in all patients before treatment and at 3-month intervals after each procedure as a general institutional protocol for this kind of patients. For the aims of this study, pre-PDT ICG angiography was used to analyze occult CNV, where careful topographic mapping of the lesion structure was prevented by the presence of masking material, such as blood or pigment. In these cases ICG disclosed hot spots or plaques, thus revealing the location of the active CNV. ICG angiography was also studied in all other patients (classic CNV) in order to evaluate any possible variable capable to predict CNV regrowth. After PDT, the presence of a choroidal neovascular net within the treated area, associated with late subretinal leakage of fluorescein, 3 months after procedure, was considered the main criterion adopted to state the presence of still active CNV. A retrospective analysis of pretreatment angiographies of all eyes, extended not only to the neovascular lesion, but also to the surrounding areas, was then carried out in order to identify signs as potential indicators of possible recurrences. The following angiographic elements have been detected: 1) fluorescein hyperfluorescence in areas surrounding the CNV, 2) pigmentary changes associated with mottled fluorescence in areas surrounding the CNV, and 3) intrachoroidal ICG staining. Shape and dimension of recurrent/persistent CNV were then compared to angiographies performed before PDT. The diameter of the laser spot used for the PDT was recorded and related to the diameter of the recurrent CNV. All these subjects respected light eviction and wore special glasses after PDT.

RESULTS

A total of 226 eyes received PDT for a predominantly classic CNV and 116 eyes for occult with no classic CNV. Three months after PDT, early frames of fluorescein angiography showed a hypofluorescence corresponding to the treatment area, which progressively disappeared during the following frames and in the late phases. In some cases this was the result of two opposite signs, the

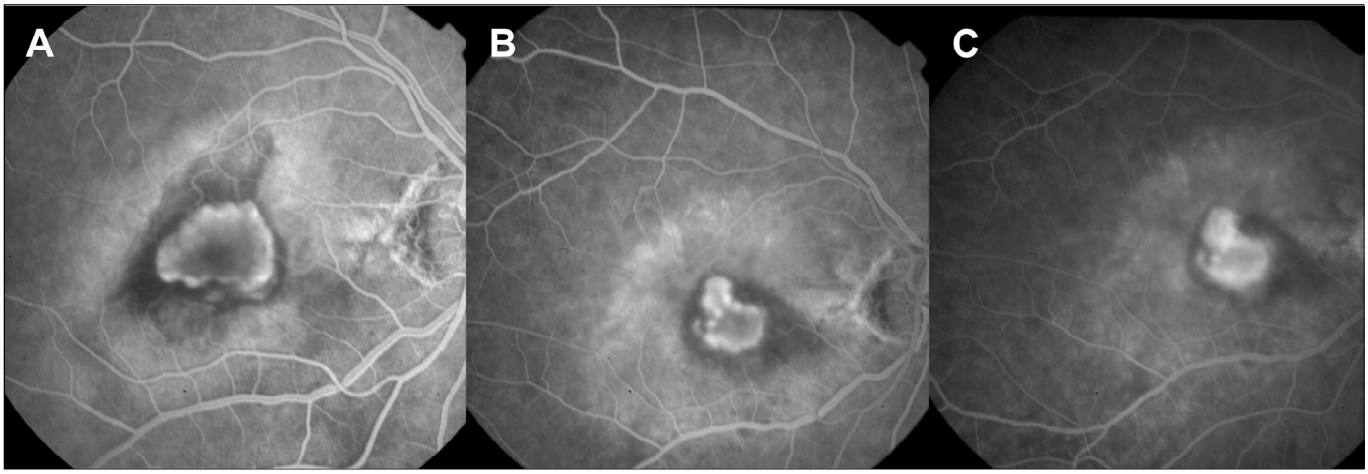

Fig. 3 - *Though in most cases recurrences take place in an area strictly related to the original membrane, they sometimes show an apparently independent arborization. Fluorescein angiography before photodynamic therapy* **A** *shows early abundant leakage;* **B** *and* **C** *show fluorescein of the same eye 3 months after treatment, with a recurrence having different features compared to the original membrane.*

TABLE I - DEMOGRAPHIC DATA AND CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

Number of patients	342	
Female (%)	207	(60.5)
Male (%)	135	(39.5)
Age, y (±SD)	73.1	(±10.3)
Type of choroidal neovascularization		
Predominantly classic (%)	226	(66)
Occult (%)	116	(34)
Mean follow-up, mo (±SD)	26	(±9)
Mean number of PDT treatments (±SD)	4.1	(±2.4)

SD = Standard deviation; PDT = Photodynamic therapy

TABLE II - CHARACTERISTICS OF PATIENTS WHO SHOWED CNV RECURRENCES RESEMBLING SHAPE AND DIMENSION OF THE PDT LASER SPOT USED IN THE PREVIOUS TREATMENT

Number of patients	23	
Female (%)	9	(39.1)
Male (%)	14	(60.9)
Age, y (±SD)	69.1	(±8.2)
Mean GLD of the lesion before any PDT, mm (±SD)	3.1	(±2.3)
Total number of PDT treatments, mean (±SD)	3.5	(±1.1)

CNV = Choroidal neovascularization; SD = Standard deviation
GLD = Greatest linear dimension; PDT = Photodynamic therapy

hypofluorescence linked to hypoperfusion and hyperfluorescence for increased transmission due to mild pigmentary changes. Persistent/recurrent CNV demonstrated late subretinal leakage of dye. ICG provided a more precise mapping of the treatment area with early and late hypofluorescence. This dark area, which was clearly associated to the shape and dimension of the spot of the PDT, showed disappearance of some choroidal vessels and rarefaction of choriocapillaris (Fig. 1). Within this area, where late subretinal leakage of fluorescein revealed persistent or recurrent CNV, early frames of ICG evidenced the neovascular net which was in most of the cases associated to late hyperfluorescence. Due to less leakage and slower perfusion of the neovascular net after PDT, dynamic angiography with the scanning laser ophthalmoscope allowed identification of a feeder vessel in 82% of the cases among those with recurrent CNV (Fig. 2). All recurrences developed in an area adjacent or corresponding to that of the previous CNV, even though shape and dimensions did not necessarily reflect those of the original membranes (Fig. 3). Thirteen cases (3.8%) developed recurrent CNV extending beyond the margins of the treatment spot, while all other membranes developed within the treatment area.

We have studied the scanning laser angiographies for analysis of the early frames, mainly referring to the filling pattern of the lesions, while for the late phases only the Topcon angiographies were considered. This decision was taken as a consequence of the well-recognized pros and cons of the two techniques. However, we did not

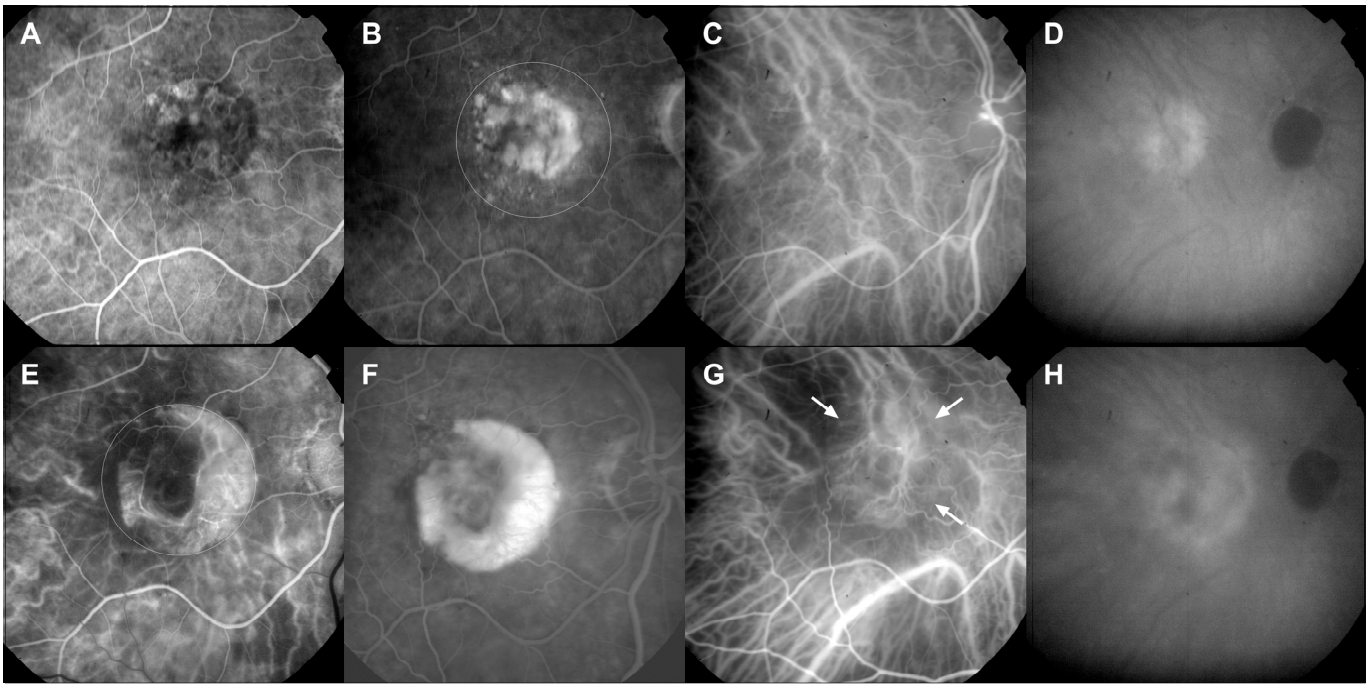

Fig. 4 - *In the pre-photodynamic therapy angiographies, a predominantly classic subfoveal choroidal neovascularization (CNV) appears to be surrounded by areas of pigment epithelial modifications ((***A***) and (***B***)). Early indocyanine green (ICG) frames confirm the presence of the choroidal new vessels (***C***), which are associated to late dye leakage (***D***). The patient was treated with PDT with a laser spot diameter of 3.8 mm (see white circle in* **B***). After 3 months a recurrence is evident, its position, shape, and diameter quite resembling those of the laser spot used for the PDT (see circle) (***E, F***). ICG angiography reveals closure of most part of the original CNV and confirms the presence of a round-shaped recurrence (arrows) (***G***), associated to late dye leakage (***H***).*

identify angiographic signs, in the pre-PDT examinations, significantly correlated to the presence of recurrences or persistences. Recurrent/persistent CNV could actually develop where pre-PDT fluorescein and indocyanine green showed 1) a leaking CNV, 2) some hyperfluorescent spots not associated to late dye leakage, and 3) a normal retina. We have studied ICG in occult CNV (116 eyes). Only in 32 eyes (9.4%) did pretreatment ICG late phases show a late hyperfluorescence exceeding any certain or questionable signs of fluorescein leakage, which seems to suggest that the high rate of persistence/recurrence cannot be explained by fluorescein underestimation of the extent of the neovascular lesion.

Twenty-three patients (6.7%) after first PDT showed a recurrent CNV which had the shape of a circle or an arch of circle (Figs. 4, 5). The mean GLD of CNV was 3.1 mm (±2.3 mm) with a mean laser spot diameter of 4.2 mm (Tab. II). The dimension of this circle corresponded in each patient to the diameter and to the position of the laser spot that had been used for the PDT. Pre-PDT angiographies showed in that area no clues of even silent CNV, but a normal appearing retina or minimal mottled pigmentation. These apparently PDT-related CNV originated from predominantly classic lesions in 15 eyes and occult lesions in 8 eyes. All other information, such as age or sex, did not significantly differ from the whole sample. Interestingly, all these particular recurrences had the features of classic lesions and showed good response to further PDT treatment.

DISCUSSION

PDT is the only treatment that has demonstrated clinically significant results in selected patients with ARMD and pathologic myopia complicated by subfoveal CNV. Major drawbacks are related to a limited and temporary collapsing effect on the neovascular membrane. Even though the mechanisms of action of PDT are not completely understood, it is commonly assumed that it creates a selective photothrombosis on the targeted CNV. However, a certain degree of temporary choroidal vessel closure can be appreciated also in territories not belonging to the CNV, albeit included in the treatment spot.

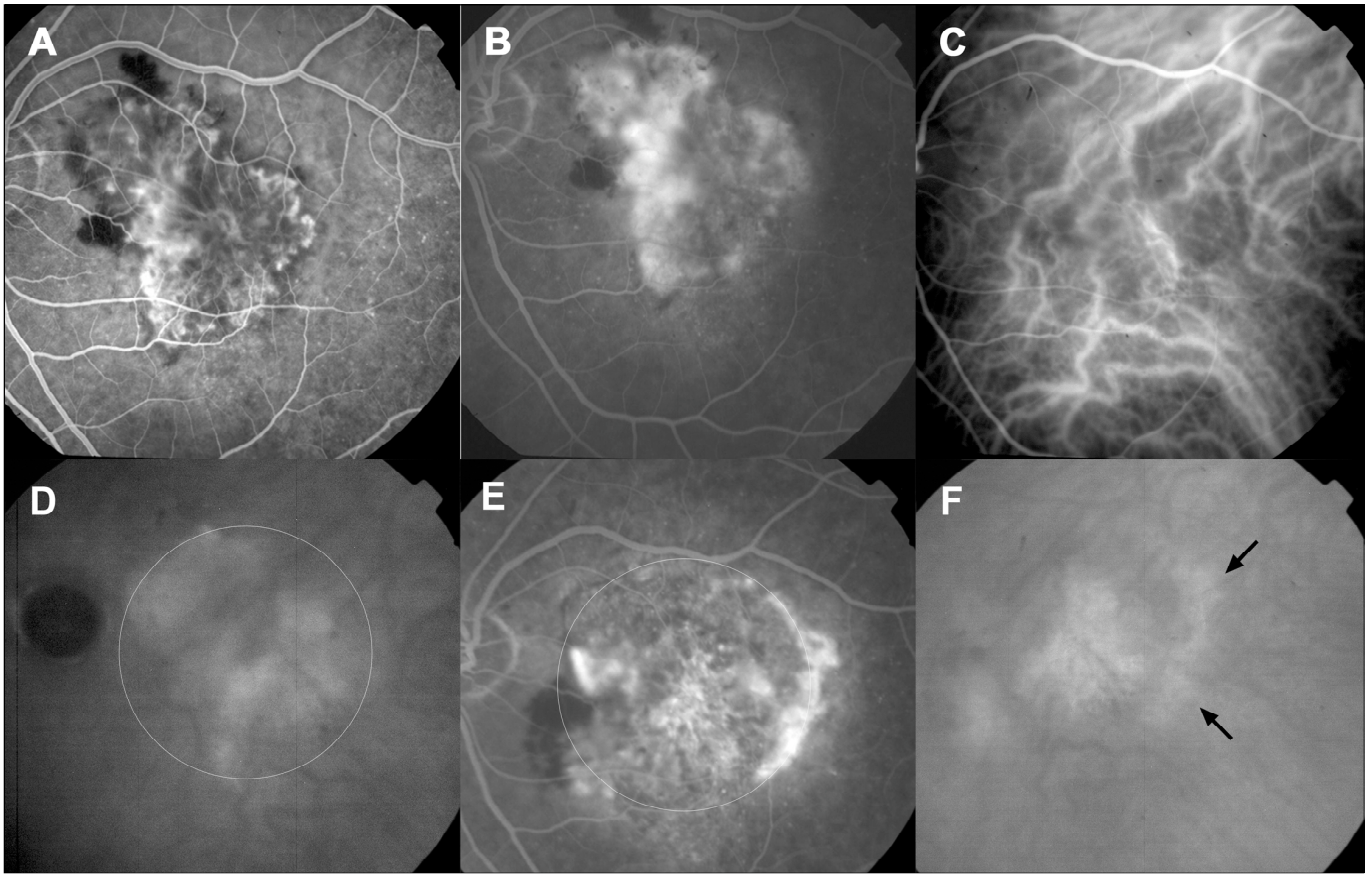

Fig. 5 - *Fluorescein angiography shows a classic choroidal neovascularization (CNV) with late subretinal leakage* (**A**, **B**)*.* **C** *and* **D** *show early and late indocyanine green (ICG) frames confirming the presence of active choroidal new vessels. The patient was submitted to PDT with a laser spot of 6.1 mm. Three months after this treatment, both fluorescein* (**E**) *and ICG* (**F**) *revealed a significant reduction of dye leakage from the original membrane while a recurrence was evident close to the temporal side of the lesion (arrows). These new vessels corresponded to an arch of circle having same diameter and position of the laser spot (see white circles).*

These side effects have already been described in different studies and have been considered related to partial selectivity of drug-mediated photothrombosis (15, 16).

Shortly after PDT, an increase of choroidal vascular permeability within the irradiated area has already been demonstrated both with angiography and OCT (6, 11). This is followed by vessel closure, well evident on new vessels but also appreciable on small and medium caliber choroidal vessels. One month after PDT, fluorescein angiography shows a hypofluorescent area corresponding to the treatment spot. From 3 to 4 weeks after PDT, a gradual reopening leads to near normal perfusion of choroidal vasculature. In most cases, however, CNV also show progressive reopening or regrowth, as demonstrated in different trials (17).

It is not clear what mechanisms control reopening of CNV closed by PDT or their regrowth within or beyond the area of the original lesion. Our study has been carried out in patients who received a mean of 4.1 PDT treatments, during a 26-month follow-up. We tried to verify if expert analysis of pretreatment angiographies could help to predict the risk of recurrent or persistent CNV. However, we have not been able to identify elements that could preoperatively provide critical information as to the probability of CNV regrowth or reopening.

ICG angiography is generally considered to be more accurate in imaging choroidal new vessels (see ARVO 2006 meeting, poster #2140 by G.J. Coscas et al). Careful analysis of pre- and post-treatment angiographies revealed that in no cases of our series did indocyanine green show more accuracy than fluorescein to state whether recurrent/persistent CNV are present or not. Nevertheless, in 9.4% of the cases indocyanine green seemed to provide a more precise topography of the CNV lesion. This may theoretically lead to underestimation of the extension of the lesion, as described by fluorescein.

However, it does not account for the high number of recurrences after PDT, which cannot eventually be explained with a lower sensitivity of fluorescein.

Three months after PDT, major choroidal vessels within the treatment area are patent and fluorescein demonstrates progressive reduction of local hypofluorescence. However, a dark area, clearly visible with ICG and corresponding to the laser irradiation spot, reveals partial rarefaction of smaller vessels and choriocapillaris. This mild vascular remodeling of choroidal vasculature within all the irradiated area could explain an increased capability to detect the feeder vessels of the choroidal neovascular membrane, compared to pretreatment angiography. In a previous study we have demonstrated that within a sample of 156 eyes treated with PDT, pretreatment dynamic angiography with fluorescein and ICG could identify a feeder vessel in only 22.4% of the cases. Three months after procedure, angiography revealed a persistent/recurrent CNV in 133 eyes. Identification of feeder vessels now rose to 84.2% of the cases (112 eyes). This has been explained with a reduction after PDT of the angiographic noise due to multilayered choroidal vasculature and with an easier detection of slower blood flow associated to actual active CNV (18).

The most striking observation of the present study is that some persistent or recurrent CNV seem to be significantly related to the laser spot that had been used for the PDT. In a small number of patients (6.7%) the size and shape of recurrences clearly reflected dimension and position of the laser spot used for the PDT. One might infer that PDT can act as a possible causative factor in the development of recurrences. According to this hypothesis, after PDT-triggered photothrombosis other mechanisms lead to local increase of factors which may stimulate vessel regrowth (22). One would then expect that this circle-shaped CNV is present in a higher frequency compared to what we have observed. The reason why this happens so rarely might simply be explained by the fact that within normal (or near normal) retina, where these atypical recurrences develop, mechanisms that control angiogenesis are more efficient than elsewhere. Thus, PDT-mediated stimulation of CNV regrowth is most of the time counterbalanced by physiologic control of angiogenesis. However, the possibility that this uncommon type of recurrence might simply be due to random image variation cannot be excluded.

According to some studies, most patients who angiographically seem nonresponders to PDT show a CNV size larger than before treatment. This enlargement generally takes place within the treatment spot area (19). It has also been histologically demonstrated that the peripheral part of a CNV is more active than the center, which increases the chance to see recurrences towards the margins of the treatment spot (20). Even if we cannot theoretically exclude that CNV was already present before PDT, though not angiographically visible, one can speculate that PDT may eventually stimulate CNV regrowth or reopening. Exact explanation of this phenomenon remains unclear but it is in agreement with those studies that have recently demonstrated that, shortly after PDT, there is an increase of permeability of choroidal vasculature (6) and upregulation of proangiogenic factors (21, 22). Interestingly, all these presumably PDT-related recurrences had the features of classic lesions, even though we do not have any reasonable explanation for that.

According to classic interpretation of the mechanisms of action of PDT, a verteporfin-mediated photothrombosis, triggered by light irradiation, leads to closure of targeted choroidal (new) vessels. It seems that PDT might also stimulate release of proangiogenic factors which can be responsible for an increased vascular permeability within the irradiated area, as well documented by OCT studies (23, 24). Shortly after PDT there is a significant increase of retinal thickness, associated to increased choroidal vessel leakage within the irradiated area, which lasts for some days. These reactions may also be the consequences of local inflammatory response after PDT.

Furthermore, there is evidence that retinal pigment epithelium shows significant alterations of intracellular organelles after PDT in animal models (25). A recent publication reported severe pigment epithelial changes in the treatment area after PDT also in human subjects (26). The retinal pigment epithelium is involved in the production of hormones, such as PEDF (pigment epithelial derived factor), which inhibits angiogenesis. Upregulation of proangiogenic factors after PDT, or downregulation of PEDF, due to pigment epithelial modifications, might imbalance the equilibrium that controls choroidal angiogenesis. This could explain the high tendency of CNV to recur, and also the appearance of the PDT-shaped recurrences.

PDT with verteporfin constituted a breakthrough in the management of CNV, the most devastating complication of ARMD. The understanding of the intrinsic mechanisms of this treatment can help to increase the clinical success rate. The observation that some limitations of this therapy might be related to a proangiogenic effect

provides a rationale for new and promising emerging strategies that associate PDT to local delivery of specific antiangiogenic drugs.

No authors have any proprietary interest.

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