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Photodynamic therapy of choroidal hemangioma: two case reports

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Abstract *Background:* Photocoagulation, cryotherapy and radiotherapy have been used to treat angiomatous lesions. Depending on the location of the angioma, these treatments can cause additional, significant functional damage. Photodynamic therapy (PDT) however, allows a selective occlusion of vascular lesions without damaging adjacent retinal structures. *Methods:* Two patients with isolated choroidal hemangiomas involving the posterior pole were treated with PDT. Treatments were performed using a diode laser at 692 nm, a light dose of 100 J/cm^2 and 6 mg/m^2 body surface area verteporfin (BPD-MA). PDT was applied in two courses in one eye and in four in the other eye at 1–4 months intervals. Patients were followed up for 9–12 months with visual acuity measurements and dilated ophthalmoscopy. Ultrasound, indocyanine green angiographic and fluorescein angiographic images were evaluated at each visit. *Results:* Tumor heights were 3.3 and 4.6 mm on pretreatment ultrasound. After therapy, patients with isolated choroidal hemangioma showed total regression of the lesion and improved visual acuity due to resorption of retinal edema. Serous retinal detachment and cystoid macular edema resolved. Ultrasound demonstrated a progressive decrease in tumor height after each PDT application, with complete disappearance of the lesion. Retinal vessels were not affected by the treatment, and retinal function recovered in areas with previous tumor involvement. *Conclusion:* PDT allows selective treatment of large intraocular angiomatous lesions.Without optimized parameters, complete regression of choroidal hemangiomas, resolution of secondary complications and improvement of visual acuity were documented.

Introduction

Intraocular angiomas are benign tumors which may become clinically symptomatic through visual distortion and central visual loss. These visual complications in angioma patients result from transudative leakage, accumulation of subretinal fluid and serous retinal detachment with secondary photoreceptor damage as well as cystoid macular edema [3, 4, 20, 21]. Although these lesions can remain stable, several authors reported progressive enlargement of tumors, which may result in total retinal detachment and blindness [20, 21]. It is recommended to monitor small asymptomatic lesions for progression or for development of exudation. If such changes occur, therapeutic intervention should be considered [17].

Various types of treatment have been described for choroidal hemangiomas as well as for retinal angiomas. Photocoagulation, cryotherapy and radiation therapy, as well as proton beam and plaque brachytherapy, have been investigated and shown to be beneficial in a number of cases [1–3, 8–10, 13, 17, 19, 23]. All these treatments share an invasive approach, and recurrence is not uncommon. Sandborn et al. [12] reported that leakage from hemangiomas reoccurred in more than 50% in pa-

tients after laser treatment. They described the visual outcome in these patients as frequently "not good". Anand et al. [3] found a poor visual outcome in the long-term follow-up in patients with anatomically favorable results as well as in patients with tumors not involving the fovea. Persisting retinal detachments following laser therapy may be retreated a second time [3, 19]. Radiation therapy or proton beam therapy, which can not be repeated after the first treatment has failed, may also cause other complications. The risk of developing osteosarcomas or soft tissue sarcomas was statistically significant in children who received radiotherapy for skin hemangiomas [6]. Cataract, radiation maculopathy and radiation retinopathy are other ocular side effects [1, 7, 17] that may be associated with all types of radiation therapy. Using plaque brachytherapy the patient has to undergo surgery twice, facing possible intra- and postsurgical complications. The benefit-to-risk ratio of these treatments is still a topic of discussion [7, 13, 17].

An ideal treatment for angioma patients would have to fulfill a number of requirements: Regression of the tumor, total retinal reattachment, minimal side effects and preservation if not improvement of the retinal function. However, depending on the location and the size of the angioma, especially when the lesion is located close to the macula or to the optic nerve head, the currently available treatments may cause additional, severe functional impairment.

Photodynamic therapy (PDT) which is currently under investigation for treating subfoveal neovascularization, offers a new approach to the treatment of these benign vascular lesions. It allows selective photochemical destruction of vascular endothelial cells only, while preserving other retinal and neurosensory structures [14]. The free-radical-induced damage of the endothelial membranes is followed by platelet adhesion and degranulation leading to thrombosis of the targeted vascular structure. Occlusion of abnormal vessels results in vascular tissue fibrosis and secondary tumor regression [15].

In a pilot study Schmidt-Erfurth et al. demonstrated complete and irreversible microvasculature occlusion of experimental choroidal tumors after PDT [14]. Based on these studies in animal models, two patients with large choroidal hemangiomas of the posterior pole were treated with verteporfin PDT. Both tumors demonstrated progression in size and extensive leakage with involvement of the fovea and subsequent visual loss. The rationale of an investigational treatment was to prevent further damage and potentially stop exudation and tumor growth.

Patients and methods

Patient selection

Two patients (two eyes), one man and one woman, with intraocular circumscribed choroidal hemangiomas were treated. Both had accompanying serous retinal detachment involving the fovea and had not had any prior treatment. These patients were referred to our clinic, because tumor size and/or location excluded them from other treatment modalities, and severe functional damage after therapy was to be expected after conventional therapy. Both patients were older than 21 years and gave written informed consent prior to their inclusion into the study. The study protocol was approved by the local ethics committee.

Photodynamic therapy

Photodynamic therapy was conducted using either a Zeiss laser ("Visulas II") or a Coherent laser ("CR-599"), both emitting light at 692 nm for photsensitization. The diameter of the treatment spot was calculated based on the lesion size measured on the pretreatment fluorescein angiogram. The maximum treatment spot diameters were 4000 µm for the Coherent laser and 6000 µm for the Zeiss laser using a Mainster wide-field lens (magnification 1.47).

Depending on the size of the lesion one to three overlapping exposures were applied during each treatment course. Treatments were repeated with changing parameters two to three times at intervals of 1–4 months. A radiant exposure of 100 J/cm^2 was applied with an exposure time of 168 s for each treatment spot. Benzoporphyrin-MA (Verteporfin) at a dosage of 6 mg/m^2 body surface area was administered intravenously before treatment. The laser beam was applied to the retina 10–15 min after the start of the infusion.

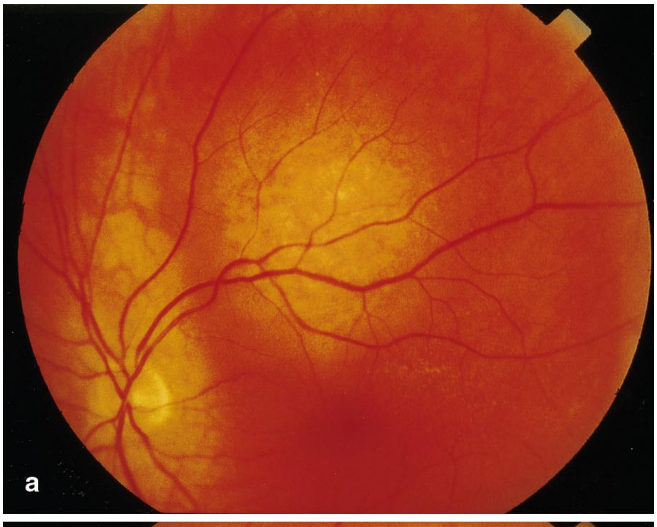
Documentation

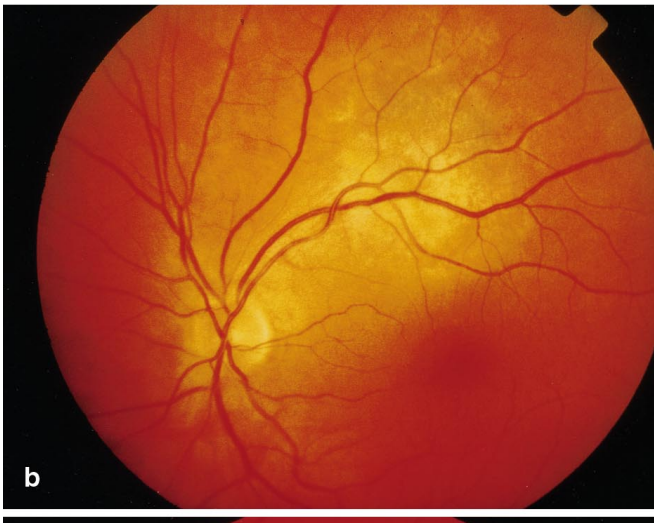
All patients underwent standardized visual acuity measurements using Landolt single optotypes at a distance of 5 m as well as the ETDRS charts at 2 m. Slit-lamp examination, intraocular pressure (IOP) measurements, dilated ophthalmoscopy and ultrasound to

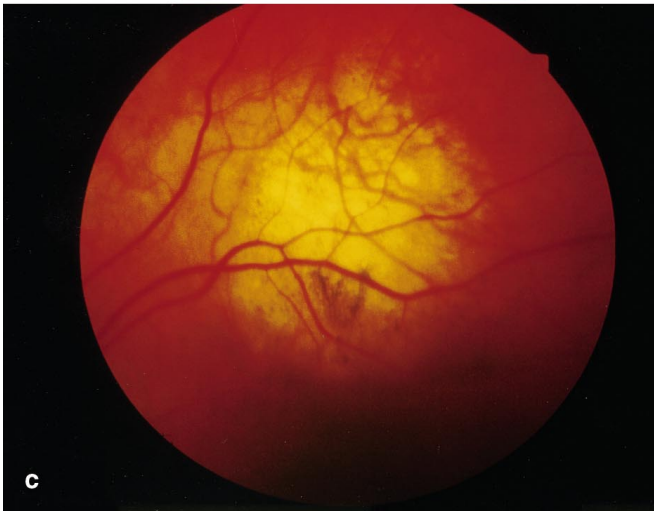
Table 1 The findings before and after photodynamic therapy regarding visual acuity, tumor height as measured by ultrasound and clinical symptoms as seen ophthalmoscopically (*CME*, cystoid macular edema)

	Location of choroidal hemangioma	Pretreatment status			Posttreatment status		
		Visual acuity	Height	Clinical symptoms	Visual acuity	Height	Clinical symptoms
Patient 1	Extrafoveal	0.5	3.3 mm	CME, central retinal detachment	1.0	0 mm	Ø CME Ø detachment
Patient 2	Subfoveal	0.15	4.6 mm	CME, peripheral serous retinal detachment	0.4 p	0 mm	Ø CME Ø detachment

document tumor extensions were performed. Color fundus photography, indocyanine green angiography (ICG-A) and fluorescein angiography (FA) were taken. All examinations were performed within 1 week before treatment and at follow-ups at 4 weeks after each treatment and at 9 and 12 months.







For FA a camera system (Olympus GRC-WT 2) was used. Pictures at a 30° angle were taken prior to dye injection and after 10 s to 2 min, 2.5 min and 10 min following i.v. administration of 5 ml of a 10% sodium-fluorescein solution. The size of the treatment spot was calculated based on the greatest linear dimension of the lesion on a 35-mm film negative angiogram with an overlaid transparency. Assuming a magnification of 2.5 for the camera used, the greatest diameter of the lesion on the retina was defined by dividing the length by a factor of 2.5. An additional distance of 500 µm was added to the resulting number to ensure coverage of the entire tumor.

For ICG-A imaging a laser scanning system (Heidelberg retina angiograph, HRA) was used. 30° frames were taken during early-phase angiography at 10 s to 2 min after injection of 40 mg of ICG (Pulsion) and during late-phase angiography at 5 and 15 min.

Ultrasound imaging was performed via an B-scan technique using an Ultrascan digital B 2000 device (Cooper Vision). To obtain accurate height data, measurements were repeated five times and special care was taken to determine the height of the tumor lesion per se, not including the overlying serous retinal detachment. Results were then averaged to obtain the tumor height in millimeters at baseline presentation and at each follow-up before an additional treatment was performed.

Results

The findings before and after treatment are summarized in Table 1.

Patient 1

Patient 1 (aged 47 years; female) presented with an extrafoveal hemangioma (Figs. 1a, 2a, 3a) with serous retinal detachment involving the fovea and decreasing the visual acuity to 0.5. Cystoid macular edema (CME) was detected clinically and substantiated angiographically. The tumor extensions measured by ultrasound were 4.6×10.1 mm with a height of 3.3 mm. A first treatment with one exposure and a diameter of 4000 µm, using a Mainster wide-field lens, was performed. Four weeks after the first treatment visual acuity had increased to 0.7 (Fig. 1b). ICG angiography showed a hypofluorescent treatment area with a rarefaction of the lacy intrinsic vessels of the tumor (Fig. 2b). The second treatment was performed because a residual tumor prominence was detected ultrasonographically and, more importantly, because persistent leakage into the macular area situated inferiorly to the tumor was still the source of substantial CME**.** After the second PDT treatment visual acuity improved to 1.0 and ultrasound detected no tumor promi-

Fig. 1a–c Fundus photography of a circumscribed choroidal hemangioma (patient 1) located at the upper vascular arcade. **a** Before treatment; **b** 4 weeks after the first treatment; **c** 7 months after the second treatment. Following treatment the subretinal fluid resolved, ophthalmoscopy showed a round fibrotic scar, and retinal structures such as retinal vessels were not damaged. Parts **a** and **b** represent 50° frames, while **c** was taken at 30°. The area showing RPE atrophy and absence of choroidal vasculature does not exceed the previous size of the original lesion and corresponds to the size of the treatment spot used

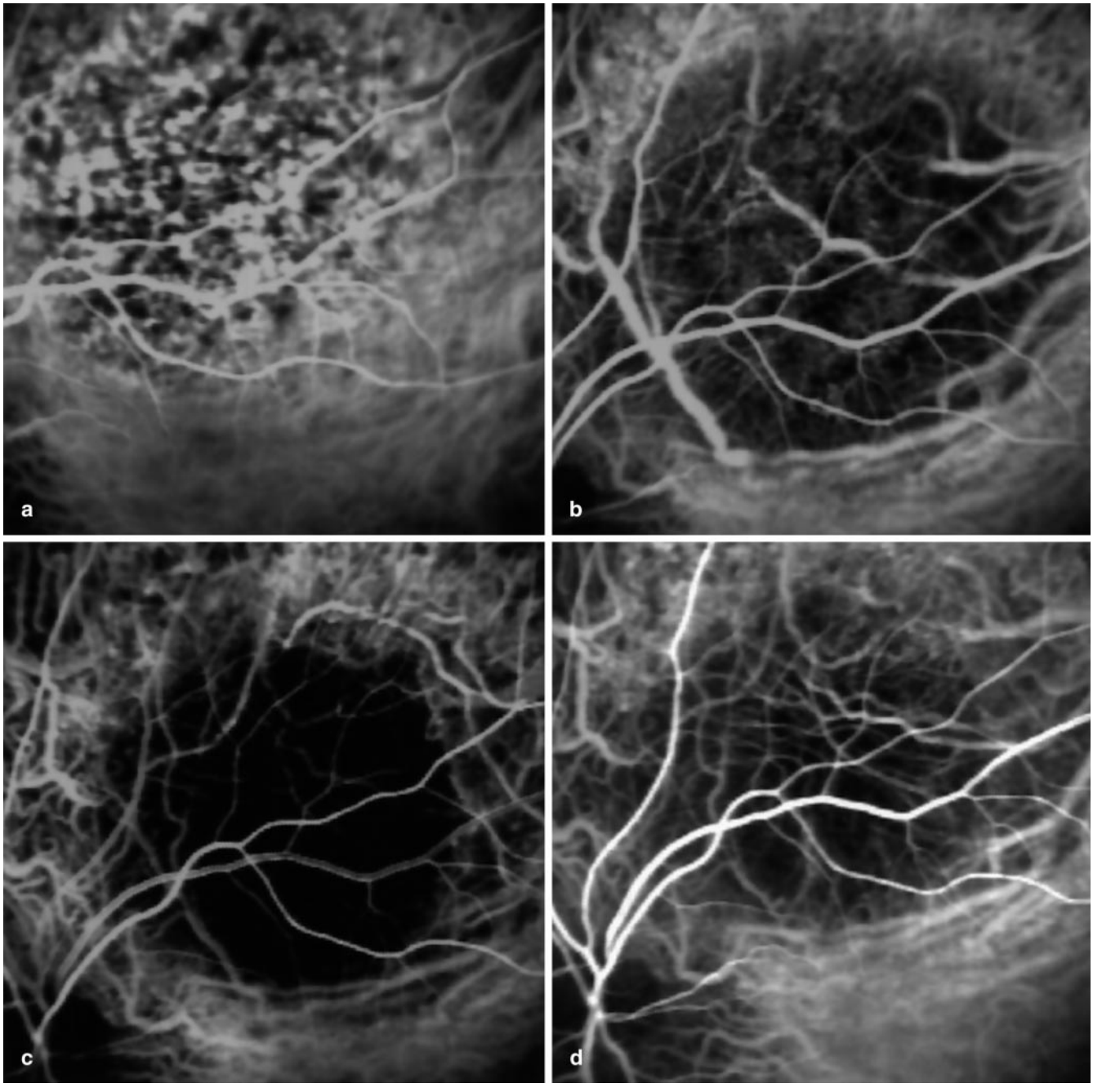


Fig. 2a–d ICG angiography (ICG-A) of the same patient (patient 1). **a** Prior to therapy, early-phase ICG-A shows typical lacy intrinsic vessels of the tumor. **b** Four weeks after the first treatment a hypofluorescent spot marking the treatment area is present, but angiomatous structures are still present. **c** Four weeks after the second treatment, total absence of tumor vasculature is shown. Physiological choroidal vessels are also absent. **d** Seven months after the second treatment: no tumor recurrence is detectable, but recovery of choroidal vasculature can be seen within the treatment area

nence (Fig. 3b). Angiographically, absence of tumor vessels was documented and a round hypofluorescent area covering the treated area was observed (Fig. 2c). No retinal nonperfusion deficits or other side effects were documented. At the 1-year follow-up visual function remained stable and ophthalmoscopy and angiography revealed no signs of recurrence (Fig. 1d). ICG angiography showed reappearance of normal choroidal vessels within the area of previous hypofluorescence (Fig. 2d).

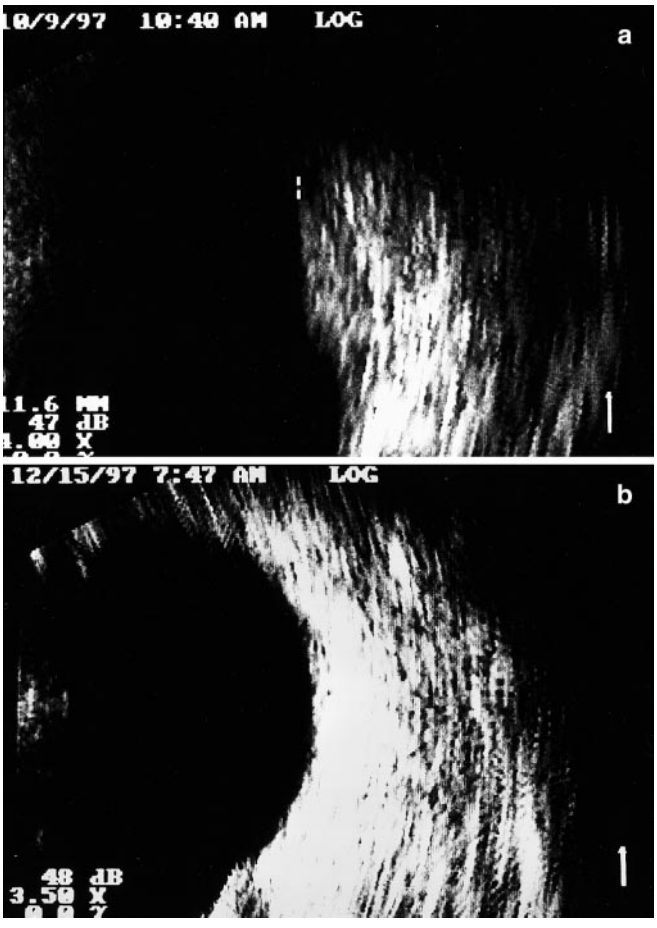


Fig. 3a,b Ultrasound documenting **a** tumor height before therapy and **b** tumor regression 2 months after treatment

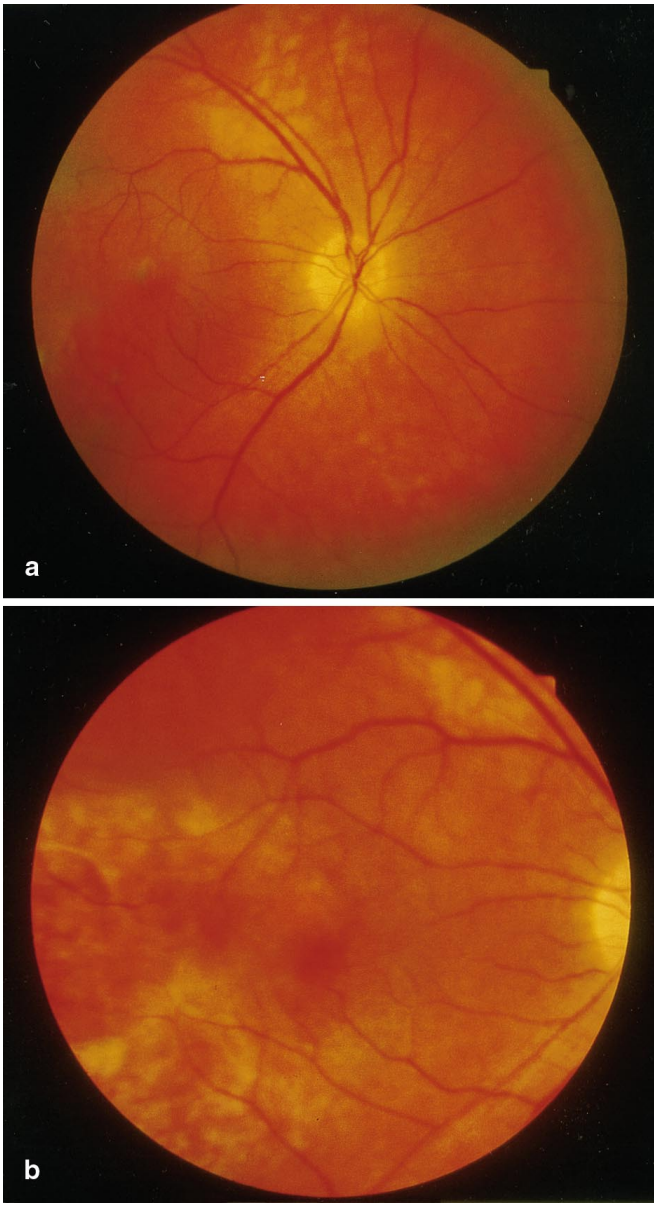


Fig. 4a,b Ophthalmoscopy **(**30° frame**)** of a large choroidal hemangioma with the central portion extending underneath the fovea and nasal part of the macula. **a** Mild RPE hyperplasia is seen near the fovea. **b** Following four treatment courses the tumor has flattened completely (50° frame). Mild RPE hyperplasia is seen in the center of the residual lesion. Some RPE changes can also be observed. However, RPE atrophy and choroidal nonperfusion, seen in patient 1 are absent

Patient 2

Patient 2 (aged 32 years; male) presented with a large choroidal hemangioma of the posterior pole covering the entire macula and extending towards the vascular arcades (Fig. 4a). The sonographic dimensions were 13.6×11.2 mm, with a height of 4.6 mm. PDT covering the entire lesion with three exposures was repeated four times at intervals of 1 month. Treatment was indicated as long as a persistent tumor prominence was delineated clinically and quantified by ultrasound measurements. Nine months after the first treatment, ophthalmoscopy revealed total regression of the tumor and visual acuity had improved from 0.15 to 0.3 (stenoptic 0.4p). FA and ICG-A documented occlusion of the abnormal choroidal tumor vessels, but the normal choroidal vessels still remained perfused. FA was performed the day prior to PDT and clearly showed active CME (Fig. 5a, b) consistent with macular edema seen ophthalmoscopically. Nine months following PDT the central retina was seen to be nonedematous clinically and CME had resorbed completely angiographically (Fig. 5c, d). Retinal vascular occlusion was not detected. Ultrasonographic examination found no measurable tumor height and the accompanying exudative retinal detachment had resolved completely. As a result of the improved visual function the patient now reported intermittent diplopia.

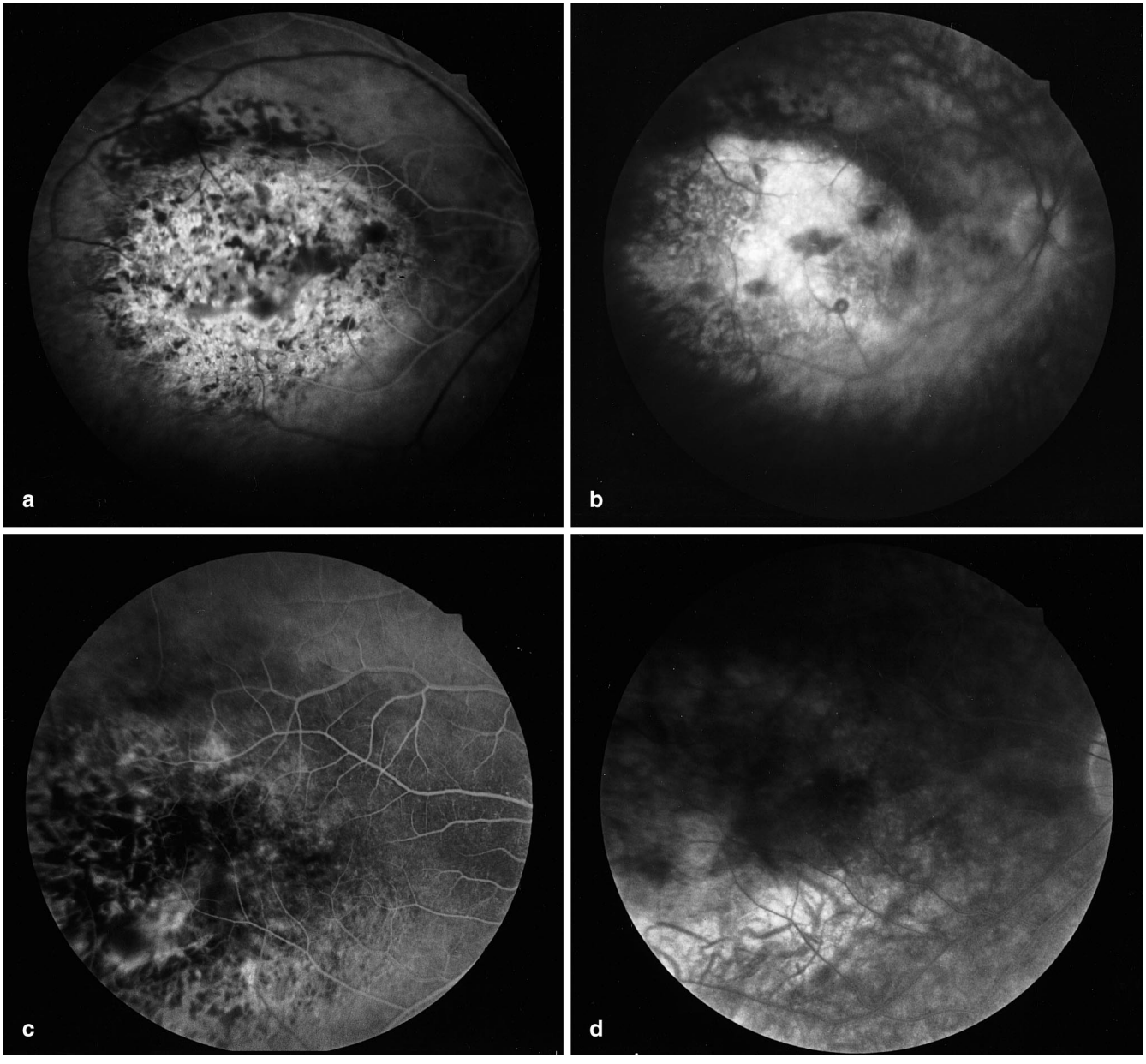


Fig. 5a–d Fluorescein angiography (FA) before treatments reveals cystoid macular edema (CME) with cystoid spaces during early FA (**a**) and leakage during late FA (**b**). Nine months after PDT CME is markedly reduced in the early phase (**c**); however, minimal CME is still seen in the later phase (**d**)

Discussion

This prospective study presents first clinical observations in treating choroidal hemangioma with PDT. PDT, originally used in tumor therapy, is currently under investigation in the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration (AMD) [15]. In view of the use of PDT in dermatology and urology, it seemed potentially promising for the treatment of intraocular tumors, which are easily accessible by laser light.

Preclinical studies showed that vascularized choroidal tumors responded with total regression to PDT treatment using benzoporphyrin [14], and occlusion of subretinal vasculature was achieved without major damage to overlying retinal structures [15]. A clinical pilot study was conducted based on experience from the first trials phase I/II investigating the use of PDT with BPD-MA in AMD [16].

Two patients with choroidal hemangioma were treated with PDT using BPD-MA (verteporfin) as a sensitizer. Generally the treatment was well tolerated; no retinal damage, nonperfusion or systemic side effects were

found after treatment. Retinal reattachment was achieved in both patients after one to four treatments. The absence of "normal" choroidal vasculature in the ICG-A image (Fig. 2c) could be interpreted as an "overtreatment effect". Obviously, the regression following PDT is a slowly progressive process and additional treatments may often not be necessary.

PDT induced a twofold benefit: the two patients with circumscribed choroidal hemangioma showed not only total regression of the tumor after PDT, but also significant improvement of the central visual acuity and the visual field due to resorption of subretinal fluid and the resolution of macular edema. At the 9-month and 1-year follow-up these patients presented without opthalmoscopically or angiographically detectable recurrence of the angioma or reappearance of serous retinal detachment. In spite of the involvement of the fovea by the pathology and the PDT, functional improvements were maintained long term.

Previous studies demonstrated that PDT had a potential benefit in tumor therapy in ophthalmology [5, 11, 18, 21]. However, results were unsatisfactory using hematoporphyrin derivate (HPD) as a photosensitizer. While some tumors showed complete regression, most lesions had only a superficial necrosis. Deeper cell layers remained viable and led to recurrence.

Significant damage also occurred in normal ocular tissue, resulting in neovascular glaucoma, iritis, hemorrhage, large areas of exudative retinal detachment and phtisis [18, 21]. One of the reasons for these significant side effects might be the low absorption peak of HDP at 630 nm and the reduced tissue penetration. Especially in prominent and highly pigmented tumors the deeper layers did not receive enough light to activate the dye sufficiently also due to the lower wavelength. The damage to normal tissue reflects a lack of sensitivity. The new photosensitizer benzoporphyrin derivate monoacid (BPD, Verteporfin), currently undergoing evaluation in a phase III clinical trial for the treatment of subfoveal neovascularizations [16], seems to be a more efficient dye than HPD. In blood, BPD binds to low-density lipoproteins (LDL), allowing selective targeting of tumor endothelium, which expresses large numbers of LDL receptors [14, 15].

BPD is also significantly more efficient but less toxic than HPD. In addition the absoption peak of BPD at 692 nm allows deeper penetration. Consequently, using BPD as a photosensitizer, a novel approach in treating intraocular hemangiomas, was expected to offer a more efficient and selective treatment.

Although the number of patients observed in this study was small, the preliminary results are promising and compare favorably with other treatment modalities. The use of photocoagulation can lead to satisfying anatomical results, but has a high risk of enhanced reaccumulation of subretinal fluid. Studies documented a large proportion of patients with poor visual outcome [3, 12]. Fractionated low-dose irradiation achieved retinal reattachment, but visual acuity again did not improve substantially even in choroidal hemangiomas, primarily a benign lesion [17]. The results of applicators such as cobalt-60 or ruthenium-106 have varied considerably. Zografos et al. found satisfactory anatomical and functional results after using a cobalt-60 applicator [23], while Kreusel et al. [9] reported an unfavorable outcome for large hemangiomas and hemangiomas associated with preexisting retinal detachment before treatment with ruthenium-106 brachytherapy. PDT, however, achieved both resolution of serous retinal detachment and visual rehabilitation in patients with circumscribed choroidal hemangiomas.

Nevertheless, the photodynamic modality is a potent vasoocclusive intervention. Care has to be taken to avoid overtreatment effects such as choroidal occlusion and subsequent RPE atrophy. Choroidal nonperfusion was after the second treatment in patient 1 and secondarily led to RPE atrophy overlying the occluded area. The dimension of RPE absence corresponded to the area presenting choroidal perfusion changes which was substantiated by comparison of fundus pictures and ICG-A images. RPE atrophy was not a primary consequence of PDT therapy per se, as demonstrated in patient 2, who underwent four treatment courses. Mild RPE hyperplasia was seen overlying the center of the lesion, where most of the tumor mass was resorbed by macrophages. RPE atrophy was not observed in this patient and choroidal perfusion was normal, despite the multiple PDT treatments.

The favorable functional and anatomical results following PDT treatment are encouraging. PDT offers a minimally invasive but effective way to treat intraocular hemangiomas. Our results suggest that PDT may be considered as a treatment modality in patients with these benign intraocular tumors, particularly when the fovea is involved either by secondary exudation or by the primary lesion. A better understanding of the photodynamic effect and its long-term results are still needed, as no data documenting the long-term effect of PDT on retinal function are yet available. Current randomized studies in AMD patients indicate that 1 year after PDT treatment no safety concerns were documented [16]. In these two patients no recurrence and no systemic or local side effects were seen after 1 year, even after repeated PDT courses. Extended studies will be needed to optimize parameters, quantify treatment effects and adequate treatment intervals, and to investigate the potential role of PDT in the treatment of malignant intraocular tumors, such as uveal melanoma and retinoblastoma.

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