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Case Study

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Severe decrease in visual acuity with choroidal hypoperfusion after photodynamic therapy

Małgorzata Figurska[ABCDE], **Joanna Wierzbowska**[EF], **Jacek Robaszkiewicz**[FG]

Department of Ophthalmology, Military Medical Institute, Warsaw, Poland

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Summary

Background: Photodynamic therapy (PDT) is considered a selective method of treatment which works in areas of choroidal neovascularization (CNV); however, there are reports of choroidal hypoperfusion after PDT. This paper presents a clinical case of choroidal circulation disturbances caused by PDT, accompanied by CNV progression.

Case Report: The patient, a 75-year-old woman, was qualified for PDT in the right eye – first treatment due to progression of occult CNV. Best corrected visual acuity (BCVA) in the right eye at baseline was +0.3 logMAR. After PDT, a rapid decrease in visual acuity to +0.7 logMAR in the right eye was observed, central choroidal hypoperfusion in fluorescein angiography (FA) with subretinal fluid appeared and, as a consequence, progression of neovascular age-related macular degeneration (AMD). After stabilizing the local state through conservative therapy, a decision was made to treat the right eye with intravitreal injections of vascular endothelial growth factor (VEGF) inhibitor. During a 12-month period of observation, 7 doses of ranibizumab were administered. A regression in activity of wet AMD was observed, with visual acuity of +0.6 logMAR.

Conclusions: Choroidal circulation disturbance after PDT is possible and has to be taken into account. Sporadically, it can lead to an acute decrease in visual acuity and local state. After stabilization of AF and optical coherence tomography imaging, further treatment of neovascular AMD with intravitreal injections of anti-VEGF agents should be considered.

key words: **occult wet AMD • photodynamic therapy • choroidal hypoperfusion • ranibizumab**

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Author's address: Małgorzata Figurska, Department of Ophthalmology, Military Medical Institute, 128 Szaserów Str., 04-141 Warsaw, Poland, e-mail: malgorzata-figurska@wp.pl

Background

Photodynamic therapy (PDT) is a 2-step procedure that combines the unique mechanism of action that a photosensitizing drug presents and a certain wavelength emitted by a non-thermal laser. First, the drug verteporfin (Visudyne®; Novartis Pharma AG, Basel, Switzerland) is administered intravenously. Verteporfin consists of lipophilic molecules, which accumulate selectively in choroidal neovascularization (CNV) foci. Its absorption peak is within long light waves, which allows them to penetrate deep tissues. The phototoxic reaction caused by PDT works within the tissues on 3 levels: cellular, vascular and immunological. The efficacy of PDT was confirmed by clinical trials, in which visual stabilization correlated with leakage from CNV being closed or limited. The selectivity of PDT has been supported by angiography, histological tests, microperimetry and electron microscopy [1]. The influence of PDT on the neovascular subretinal membrane, choroid, healthy retina at the limits of CNV foci, and retinal pigment epithelium (RPE) has been analyzed. PDT is considered a selective method of treatment which works in areas of CNV; however, there are reports of choroidal hypoperfusion after PDT or combined therapy with vascular endothelial growth factor (VEGF) inhibitors [2–4].

This paper presents a clinical case of choroidal circulation disturbances caused by PDT, accompanied by CNV progression. Functional and morphological stabilization of wet AMD over a 12-month period was achieved in this case after introduction of anti-VEGF agents.

Case Report

In December 2008 the patient, a 75-year-old woman, was qualified for photodynamic therapy in the right eye – first treatment due to progression of occult choroidal neovascularization. Best corrected visual acuity (BCVA) at baseline, tested with the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, was: right eye +0.3 logMAR (72 letters), left eye +1.0 logMAR (34 letters). Ophthalmoscopic examination of the right eye showed a grayish, elevated focus of wet AMD in the macula (Figures 1–3), and in the macula of the left eye a PDT scar was visible (3 treatments without complications in 2007). General diseases reported by the patient were arterial hypertension and stroke in the previous year. Fluorescein angiography (FA) was performed using the Heidelberg Engineering HRA 2 device, optical coherence tomography (OCT) with SOCT Copernicus HR and OCT SLO OTI. In photodynamic therapy of the right eye, the following parameters were employed: laser focus diameter 4900 μm (including a margin of healthy retina – 1000 μm), BSA 1.7, 10-minute infusion of verteporfin solution (2 mg/ml, 6 mg/m^2). The procedure began, as recommended by the standards, 15 minutes after start of the infusion; a 689 nm laser was used (Opal Photoactivator, Coherent), exposure time 83 seconds, energy 50 J/cm^2.

On the next day the patient was discharged from the Clinic with the following advice: avoid light exposure for 48 hours, use topical non-steroid anti-inflammatory drugs in the right eye, ophthalmological control in 5–7 days. Two days later the patient reported urgently to the ophthalmologist due to significant decrease of vision in the right eye. She had followed all advice according to the treatment card. BCVA

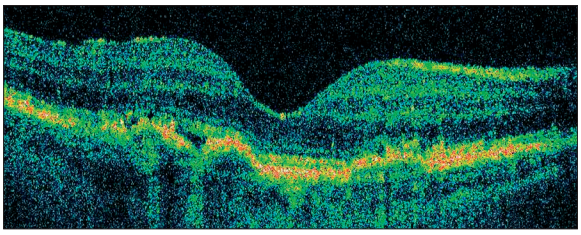

Figure 1. OCT before PDT (fovea scan): foveal contour is preserved, the highly reflective complex of RPE and choriocapillaries is irregular and thickened, subretinal fluid is observed.

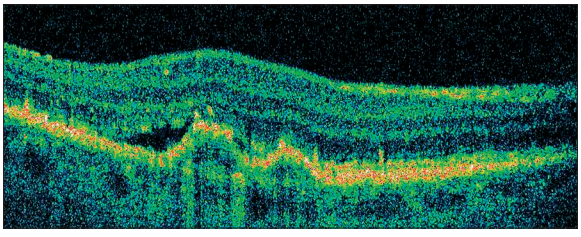

Figure 2. OCT before PDT (temporal scan): subretinal fluid and focus of occult CNV.

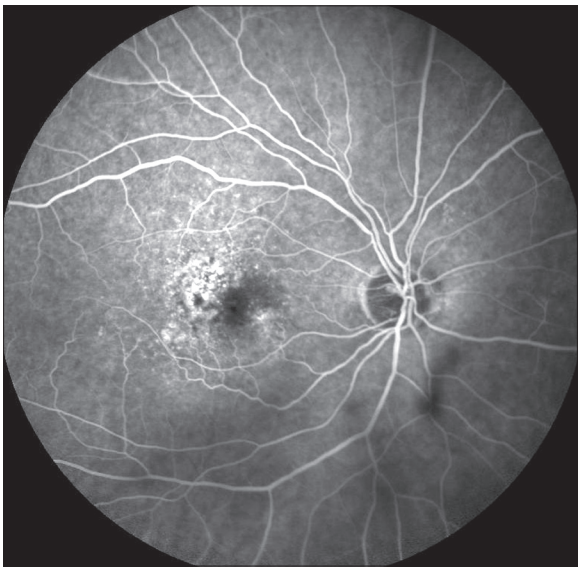

Figure 3. FA before PDT (late phase): at the macula there is ill-defined area of hyperfluorescence that does not correspond to the early phase of the angiography. Occult choroidal neovascularization, type 2.

in the right eye was +0.7 logMAR (49 letters) in a certain head position. In the fundus of the right eye, in the macula and adjacent upper temporal region, subretinal fluid was present, and ophthalmoscopic examination showed elevation of sensory retina reaching the fovea and small hemorrhages. Treatment was introduced: steroid into the Tenon's capsule of the right eye, generally carbonate anhydrase inhibitor, topically non-steroid anti-inflammatory drugs. In FA, from the early stages of the examination, a hypofluorescence focus in the macula was visible – roundish and of size and localization of the laser focus used in PDT (Figures 4, 5), corresponding with central choroidal hypoperfusion. No disturbances in blood perfusion in the

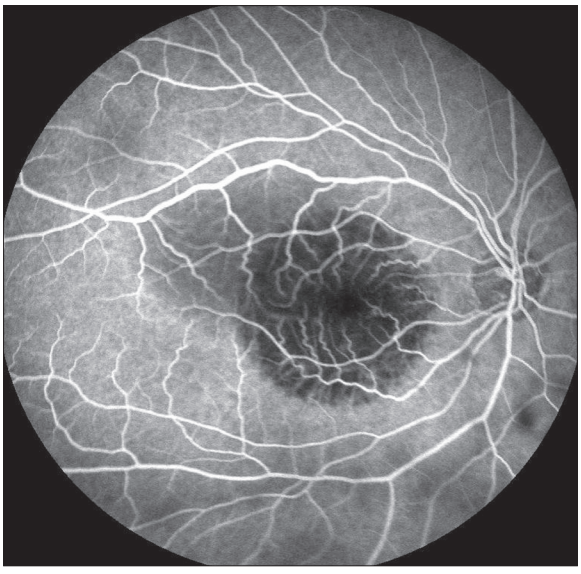

Figure 4. FA with homogenous hypofluorescence four days after PDT.

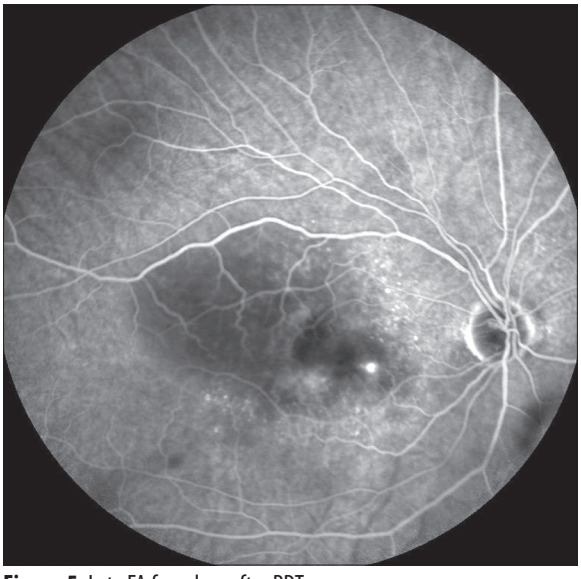

Figure 5. Late FA four days after PDT.

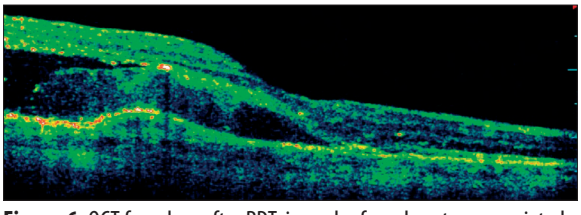

Figure 6. OCT four days after PDT: irregular foveal contour associated with extension subretinal fluid space with the fibrin in the temporal and superior part of the macula.

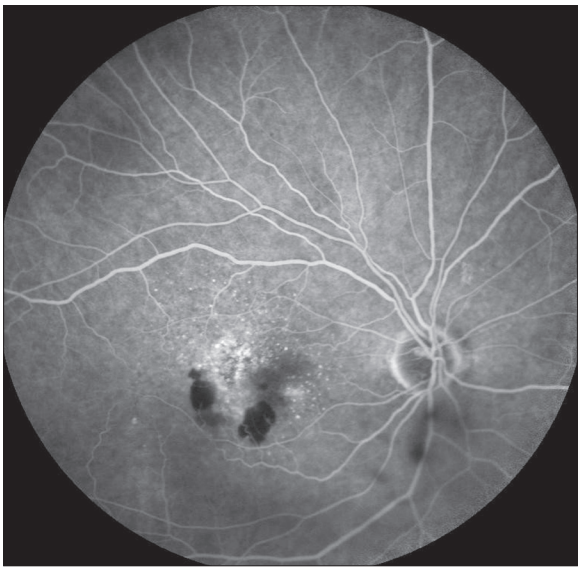

Figure 7. FA three weeks after PDT (late phase): increased hyperfluorescence is visible at the macula. A blockage beneath and temporal to the fovea is caused by subretinal hemorrhage (progression of CNV).

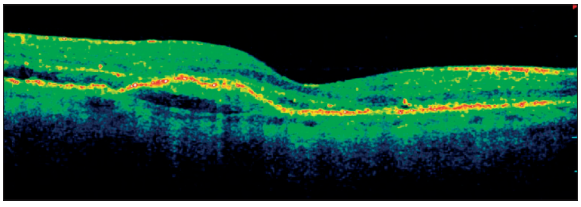

Figure 8. OCT three weeks after PDT: subretinal fluid space decreased, foveal contour is mostly preserved, focus of flat PED is present.

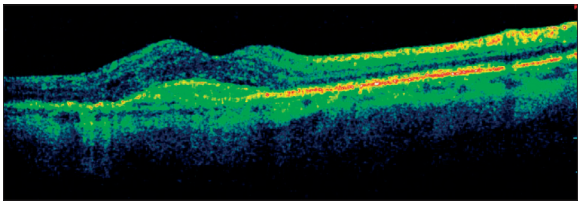

Figure 9. OCT after 12-months observation and after eight ranibizumab injections: highly reflective scar is observed in the fovea, without subretinal fluid and retinal edema.

retinal vasculature were observed. In OCT of the right eye an extensive, high elevation of retinal fluid, comprising the fovea, was seen (Figure 6). The patient was admitted to the Clinic again. Additional treatment was introduced: vitamin C, calcium and methylprednisolone (Solu-Medrol® Pfizer Manufacturing Belgium N.V., total dose 2000 mg) intravenously, drugs to tighten vessels. During the hospitalization, stabilization of visual acuity in the right eye and OCT image was achieved. After 7 days the patient was discharged from the Clinic with diagnosis of choroidal perfusion disturbances after PDT and continuation of treatment was recommended. Visual acuity in the right eye at discharge day was +0.7 logMAR (53 letters). Subretinal fluid was still present in the macula, and ophthalmoscopy showed elevation of sensory retina reaching the fovea.

In January 2009 the patient presented for control. Visual acuity in the right eye was +0.5 logMAR (60 letters), small subretinal hemorrhages in the right eye fundus were observed, subretinal fluid had significantly withdrawn. Control

FA was performed. Choroidal perfusion had returned, but increased activity of occult AMD in the right eye, compared with initial examination, was detected (Figure 7). In OCT significant withdrawal of subretinal fluid with partially reproduced contour of the fovea was observed (Figure 8).

Three months later, in April 2009, due to progression of neovascular degeneration with small fresh subretinal hemorrhages in the patient's only functional eye, a decision was made to begin treatment with intravitreal ranibizumab (Lucentis®, Novartis, Basel, Switzerland). At the beginning of ranibizumab treatment, visual acuity in the right eye was +0.7 logMAR (50 letters), and OCT image and angiography indicated activity of the process. Treatment was performed according to the following scheme: saturation phase (3 0.5 mg doses of ranibizumab at monthly intervals), with further doses according to activity of the degenerative process. At follow-up 1 month after the fourth dose of ranibizumab, visual acuity in the right eye had improved to +0.5 logMAR (61 letters), and at that time no CNV activity was seen on OCT. During the 12-month follow-up period from April 2009 to March 2010, a total of 7 doses of ranibizumab were administered to the right eye. Subsequently, no activity of the neovascular process was shown on OCT (scarring) and angiography, subretinal hemorrhages had been absorbed and visual acuity was +0.6 logMAR (55 letters) – 17 letters less than prior to PDT (Figure 9). No local complications, including disturbances in choroidal perfusion, or systemic complications were observed during the therapy. The patient remains under observation and further intravitreal ranibizumab injections are recommended in case there is any relapse of the disease.

Discussion

In a time of widespread use of anti-VEGF agents, photodynamic therapy remains a recognized method of treating predominantly classic form of CNV, as well as progressive occult CNV not larger than 4 MPS DA [5]. In this case, the basis for PDT qualification was a decrease in visual acuity, correlating with occult CNV progression on OCT and FA in a patient after stroke, who had also undergone prior PDT procedures in the fellow eye without complications.

In FA, hypoperfusion after PDT typically manifests as a moderate hypofluorescence of the altered area and a reduction in fluorescence of choroidal vessels [6]. In our case, hypoperfusion in the PDT-treated area correlated with an acute decrease in visual acuity and appearance of a large subretinal fluid space in OCT; in further observation it resulted in progression of neovascular AMD. Hypoperfusion in FA persisted for approximately 3 weeks, and return of choroidal circulation correlated with an improvement in visual acuity and OCT image.

Michels and Schmidt-Erfurth have described 3 cases in which areas of weakened perfusion were present after PDT [7]. Recchia et al. have analyzed reasons for a decrease in visual acuity of 2 ETDRS chart lines or more in 10 of 1894 eyes which had undergone PDT [4]. In 5 cases, choroidal hypoperfusion was detected in the laser therapy focus. Hypoperfusion persisted for over 4 months, and the researchers consider it a consequence of chronic or irreversible damage to choroidal function.

Indocyanine green angiography (ICGA) routinely shows hypofluorescence after PDT, which confirms that this kind of treatment results in occlusion of choriocapillaries. For example, a 6- to 12-month follow-up of PDT with ICGA in 16 eyes with central serous chorioretinopathy revealed hypoperfusion in choriocapillaries, which persisted for 2–12 months. There was no evident connection between duration and intensity of hypoperfusion and changes in visual acuity [2]. A prospective evaluation of 9 eyes which had undergone PDT due to subfoveal wet AMD showed closure of CNV leakage in OCT and ICGA in correlation with various degrees of hypoperfusion in the treated area; normal perfusion in ICGA returned within 3 months [8].

There is some evidence of a connection between post-PDT hypoperfusion and adverse effects of verteporfin therapy. An analysis of 14 patients with acute decrease in vision (loss of 20 or more letters within 7 days after PDT) in clinical studies of verteporfin showed serous macular detachment and abnormal choroidal hypofluorescence (as in our case) only in 3 patients [9]. According to this data, hypoperfusion cannot be regarded as the most important factor in acute visual loss after PDT, and the risk of choroidal ischemia secondary to post-treatment hypoperfusion is extremely low in the PDT group. Isola et al described choroidal ischemia in 2.1% of eyes treated with PDT due to wet AMD and in 0.9% due to CNV in high myopia [10]. In 12-month follow-up, visual acuity in eyes with AMD and ischemia decreased by a mean of 3 lines and there were no cases of acute visual loss of 6 lines or more.

Hypofluorescence in FA is typically connected with closure of CNV leakage after treatment. After PDT, hypofluorescence in the treated area can also be a result of reduced blood flow in nourishing vessels which maintain perfusion within CNV. In a study of 38 eyes which had undergone 1 PDT procedure and 12 eyes after several procedures, ICGA showed closure of CNV vessels and normal choroidal vessels due to action of verteporfin; while some CNV tributary vessels stayed open [11]. The potential to stimulate new vessel growth secondarily to closure of collateral choroidal vessels was illustrated in a study of 53 eyes with neovascular AMD which had undergone PDT. In this study, 3-dimensional topographic angiography showed that CNV occlusion was connected with immediate extensive exudation due to closure of collateral choroidal vessels [12]. In our case, too, subretinal exudation was observed in correlation with hypoperfusion. Occlusion with perfusion disturbances affects physiological choriocapillaries and the neovascular net for a period of 3 months after PDT. Ischemia and inflammation secondary to occlusion of choriocapillaries breaks down the vascular barrier and results in proangiogenic response with VEGF expression [13]. This correlation between PDT and increased VEGF's level justifies use of combined therapy of PDT and anti-VEGF agents in treatment of wet AMD. In our case, after PDT complicated by abnormal choroidal circulation, CNV progression was observed shortly thereafter, and a decision was made to use intravitreal anti-VEGF agent. Introduction of ranibizumab treatment allowed us to stop activity of the disease and stabilize visual acuity, which nevertheless didn't return to values found before PDT.

There are attempts to reduce post-treatment hypoperfusion through modification of PDT parameters [14]. A potential

alternative to reduction of PDT energy is reducing the dose of verteporfin or laser exposure time. Another possibility is reduction in laser focus size through reduction of the healthy retina margin to 500 μm, based on a major finding that lesion size is the most important prognostic factor of post-treatment visual acuity, and this closely correlates with laser focus size (in our case the diameter of laser focus was 4900 μm). A lower concentration of verteporfin can be achieved through an extension of the period between drug administration and laser exposure [15].

Conclusions

Clinical studies have confirmed that verteporfin photodynamic therapy is a safe method of treatment; nonetheless, hypoperfusion in the treated area is well-documented and can even persist for a few months. As our clinical case shows, a possibility of choroidal vessel occlusion with FA hypofluorescence, acute decrease in visual acuity and worsening of local state, must be taken into account. After stabilization of FA and OCT image, further treatment of neovascular AMD with intravitreal anti-VEGF agents should be considered. It is also worth considering modification of PDT parameters, especially in occult CNV cases.

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