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SHORT COMMUNICATION

Systemic bevacizumab for retinal angiomatous proliferation associated with retinal pigment epithelial detachment

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PURPOSE. *To report the off-label use of systemic bevacizumab in a patient with stage 3 retinal angiomatous proliferation (RAP) associated with a vascularized pigmented epithelium detachment (PED).*
METHODS. *Interventional case report.*
RESULTS. *The patient was treated with systemic bevacizumab after obtaining fully informed consent. At 3 months post-treatment, the authors observed an improvement of one line (seven letters) in visual acuity and total regression of the PED on ocular coherence tomography. No adverse effects were observed.*
CONCLUSIONS. *Systemic bevacizumab therapy appears to be safe and effective in the treatment of RAP associated with PED during this short follow-up period of 3 months. The authors recommend a large trial with long-term follow-up to confirm the promising results and evaluate the occurrence of adverse effects associated with systemic bevacizumab. (Eur J Ophthalmol 2007; 17: 987-91)*

KEY WORDS. *Optical coherence tomography, Pigment epithelial detachment, Systemic bevacizumab*

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INTRODUCTION

Retinal angiomatous proliferation (RAP) with pigment epithelium detachment (PED) is a distinct form of neovascular age-related macular degeneration (AMD) with a very severe prognosis. This variant of neovascular AMD is characterized by the proliferation of a retinal vascular anomalous complex leading to intraretinal and subretinal neovascularization with retinal arteries feeding and retinal veins draining the retinal vascular anomalous complex (1). PEDs are associated with this disease (serous PED in stage 2 and vascularized PED in late stages) (1). Many reports have indicated that these lesions are very difficult to treat and are associated with a poor prognosis in spite of using different treatment modalities such as verteporfin–photodynamic therapy (PDT) and combined PDT with intravitreal steroids (2, 3). Intravitreal anti–vascular endothelial growth factor (VEGF) is a new therapeutic option but, like verteporfin–PDT, has a risk of retinal pigment epithelium (RPE) tear. We report our experience of using systemic bevacizumab in a patient with this condition.

Case report

A 72-year-old woman was referred to us in May 2005 because of longstanding (more than 1 year) and progressive RAP associated with a PED, four disc areas in size, and surrounded by a ring of hard exudates in her left eye. The

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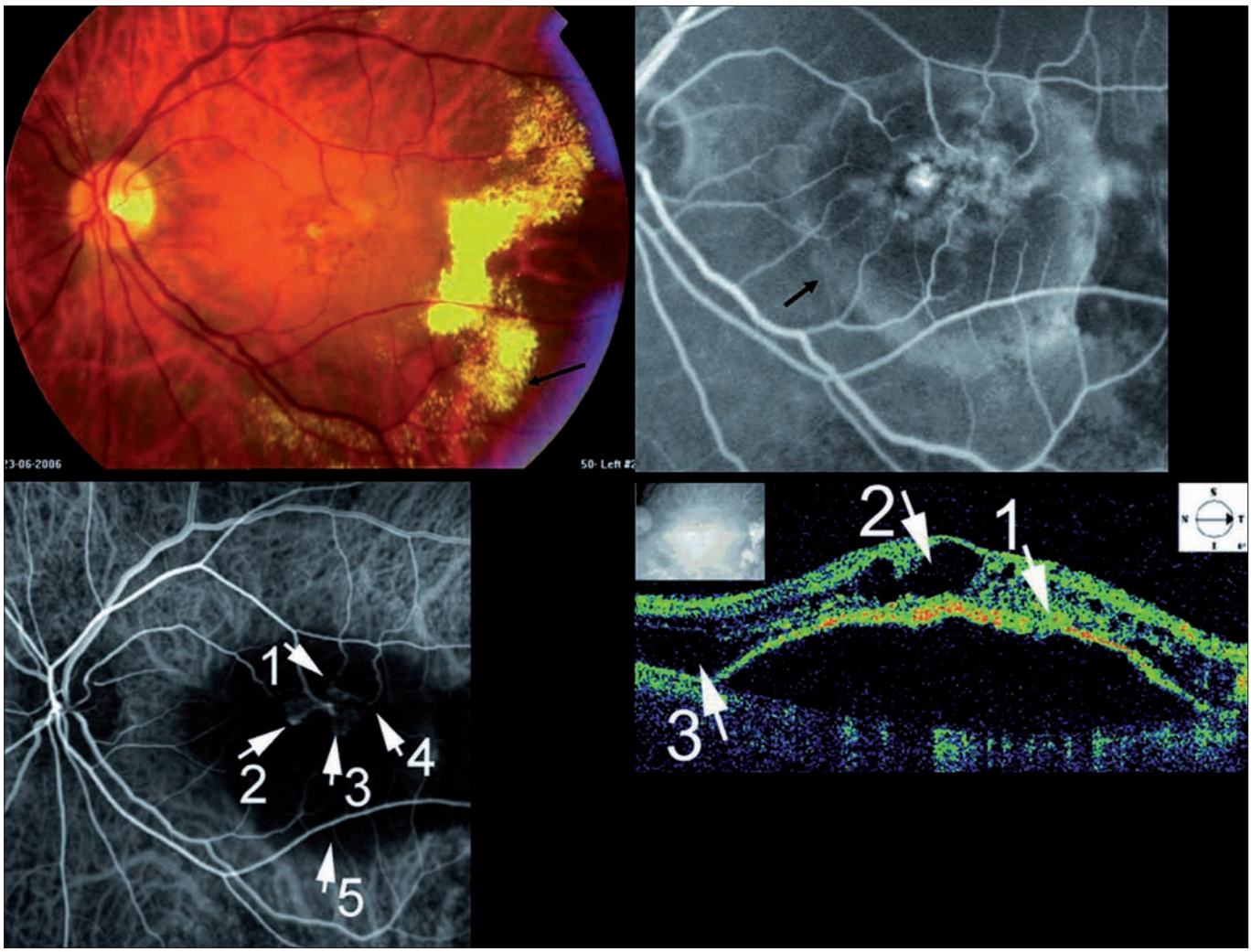

Fig. 1 - Top left: *Color photograph at the initial examination shows a retinal pigment epithelium detachment (PED), 4 disc areas in size, surrounded by a large ring of hard exudates (arrow).* **Top right:** *Fluorescein angiogram, taken with the Heidelberg Retinal Tomograph (HRT2), at the initial examination at 4 minutes, shows the large PED with hyperfluorescent borders (arrow) and poorly defined hyperfluorescent areas of leakage in its center.* **Bottom left:** *Indocyanine green angiogram (intermediate phase) at the initial examination. Note the retino–retinal anastomoses (arrows 1, 2, 3, 4) linked to a large subfoveal neovascularization in the center of a large PED (hypofluorescent area, arrow 5).* **Bottom right:** *Horizontal optical coherence tomography (OCT) cross-section taken at the same time. Note the dome-shaped elevation of the retinal pigment epithelium, thinner at the edge but with no sign of tear (not visible on all sections), and the retinal angiomatous proliferation visible at the bottom of the PED (arrow 1). Exudation is present with cystoid intraretinal edema (arrow 2) and serous detachment (arrow 3) above the lesion.*

right eye had been complicated by a RPE tear after verteporfin–PDT treatment a few months earlier. At referral, the patient read 1 letter on the ETDRS chart (<20/400) with the right eye and 20 letters (20/200) with the left eye. The left eye retina was not treated at this time because of the longstanding RAP lesion, the absence of known treatment able to improve visual acuity, and the potential risk of RPE tear that could worsen the patient's state. She had bilateral mature cataracts which were operated to restore at least the peripheral visual field. Immediately after cataract surgery, visual acuity improved to 7 letters (20/400) in the right eye and 35 letters (20/100) in the left eye.

The patient was regularly examined following her surgery; during re-examination in June 2006, her ophthalmologist observed significant changes in the left eye on fundus examination and angiographies – increased exudation and neovascular activity. At this time, she was able to read 7

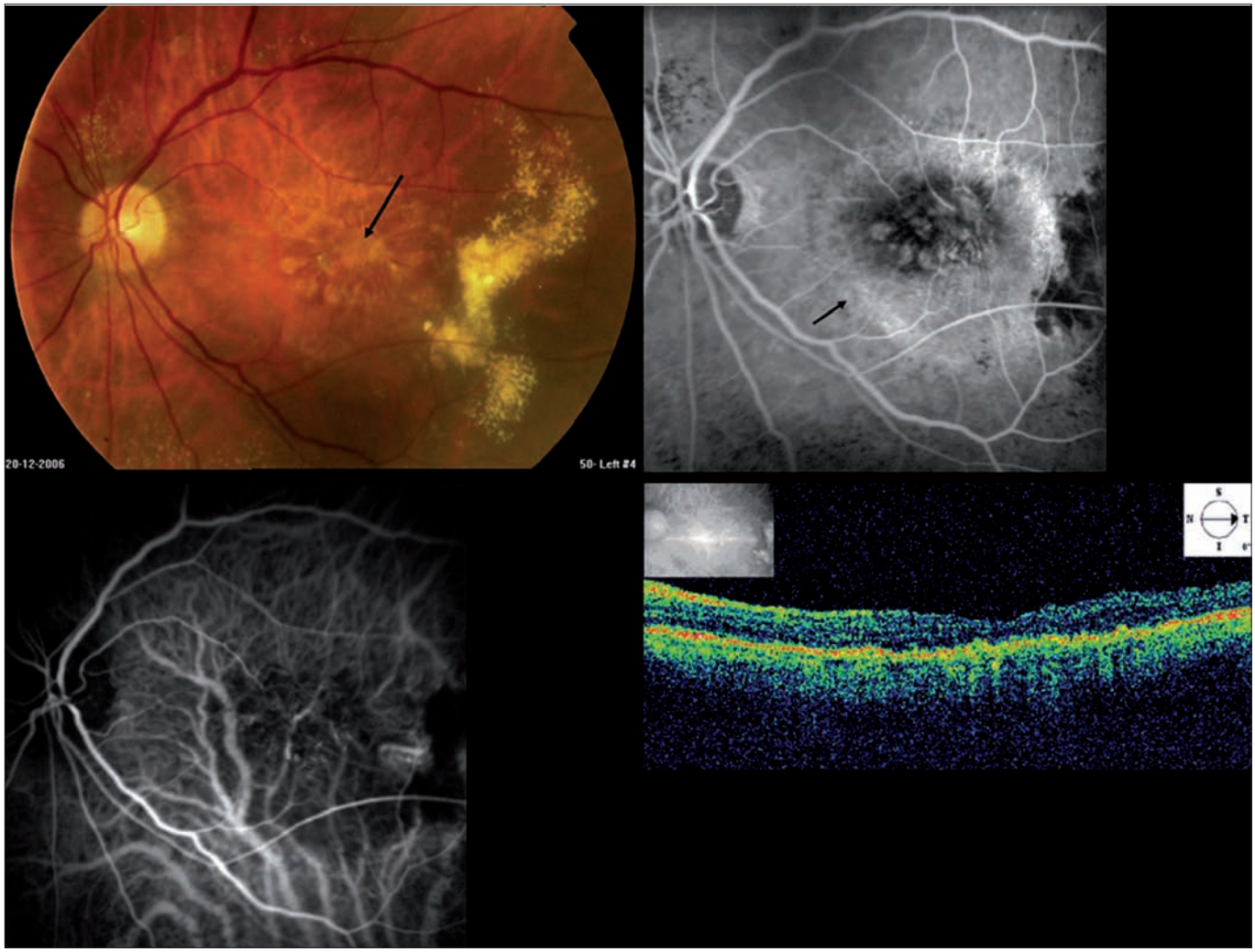

Fig. 2 - Top left: *Color photograph 3 months after the first bevacizumab treatment. The retinal pigment epithelium (RPE) detachment has disappeared, hard exudates have decreased, and the retinal angiomatous proliferation (RAP) has been replaced by a thin fibrotic scar (arrow).* **Top right:** *Fluorescein angiogram, taken at 4 minutes, 3 months after the first bevacizumab treatment shows the former pigment epithelium detachment (PED) (arrow), modifications of the RPE with thin folds, and hyperfluorescent areas but without leakage.* **Bottom left:** *Indocyanine green angiogram (intermediate phase) 3 months after the first systemic bevacizumab treatment. The RAP has disappeared; only a light hypofluorescent area remains.* **Bottom right:** *Optical coherence tomography cross-section 3 months after the first bevacizumab treatment. Note the normal appearance of the PED.*

letters (20/400) with the right eye and 30 letters (20/125) with the left eye; her contrast sensitivity (Pelli-Robson charts) was 1.05 in the right eye and 1.35 in the left eye. Color photograph of the left eye showed a PED surrounded by a large ring of hard exudates (Fig. 1, top left). Fluorescein angiogram (FA) showed a large vascularized PED with hyperfluorescent borders and poorly defined hyperfluorescent areas of leakage in its center (Fig. 1, top right). Indocyanine green angiograms (ICGA) demonstrated retino–retinal anastomoses linked to a large active subfoveal neovascularization within the PED (Fig. 1, bottom left). Ocular coherence tomography (OCT) scans showed intraretinal edema with a central retinal thickness of 404 µm and a serous detachment associated with a bulky PED; the RPE at the edge of the PED was very thin (Fig. 1, bottom right) indicating the high risk of RPE tear.

We decided to use intravenous bevacizumab treatment in this patient instead of the intravitreal route in order to

avoid the risk of ocular hypertension. After having obtained fully informed consent of the patient, and with medical cover provided by an oncologist, three intravenous bevacizumab injections (dosage of 5 mg/kg/day with a 2-week interval between each injection) were administered consistent with previous publications and the posology used in the treatment of metastatic colon cancer (4).

Our patient was regularly checked by the oncologist before, during, and after each injection for systemic adverse effects. A month after the first systemic bevacizumab administration, we observed a significant improvement of one line in the visual acuity of the left eye (to 35 letters; 20/100) and also in contrast sensitivity (to 1.5, Pelli-Robson chart). At this time, biomicroscopy and angiography showed a reduction in exudation and a clear decrease in PED size. OCT showed a decrease in PED height and regression of the serous retinal detachment and edema. The patient was then examined 3 months after the first injection when visual acuity had slightly improved to 37 letters while contrast sensitivity remained at 1.5. On the color photograph, the new vessel was replaced by thin fibrous tissue (Fig. 2, top left). There was no further exudation on FA (Fig. 2, top right). ICGA (Fig. 2, bottom left) showed disappearance of the RAP, absence of a hot spot, and a slight hypofluorescence at the former site of the PED. On OCT, there was a complete flattening of the PED with the absence of any serous retinal detachment or retinal edema (Fig. 2, bottom right). The use of bevacizumab was well tolerated with the absence of any notable elevation of blood pressure.

DISCUSSION

Currently the prognosis of RAP with PED remains poor irrespective of the chosen therapeutic option with long-standing RAP lesions requiring a particular approach. Photodynamic therapy with verteporfin (V-PDT) is not indicated in this condition due to the very high risk of a RPE tear. This complication has been described spontaneously, following V-PDT, or after any intravitreal injection. As our patient had already experienced a RPE tear in the fellow eye, the risk of RPE tear in the second, i.e., left eye is high, around 80% during 3 years of follow-up (5).

Although the causative physiopathologic mechanism of RPE tears is not fully clarified, it appears that rapid resorption of the sub-RPE fluid and tissue contraction due to the choroidal new vessel scarring may increase the shear forces within the RPE leading to a tear (6, 7). Fortunately, there was no RPE tear in our patient after 3 months of follow-up although all conditions to have this complication were present (rapid fluid disappearance and large mature choroidal new vessels).

Systemic bevacizumab, already used by some ophthalmologists for wet AMD with good results and tolerance, appears to be a suitable treatment for these patients (8). A recent non-controlled evaluation suggested the efficacy of systemic bevacizumab in treating PED using doses of 5 and 2.5 mg/kg/day in three injections separated by an interval of 2 weeks between each injection. A clear improvement was noticed in all the nine eyes presenting PEDs (8 due to CRA), after a follow-up of 3 months, in terms of visual acuity and regression of lesions on angiography and OCT (consistent reduction in the height and surface of the PED). These improvements were observed as early as the first checkup just 1 week after the first injection. Also, systemic bevacizumab was well tolerated in all of the cases with no RPE tears (9).

In our patient, angiographic pictures and OCT scans showed an anatomic and functional improvement as soon as 1 month after the first injection with the improvement persisting during the follow-up of 3 months. The visual acuity benefit was relatively low, only one line of improvement, due to the size of the PED and the chronicity of the lesion. However, the patient reported significantly better visual comfort due to the disappearance of retinal edema.

Our preliminary results with systemic bevacizumab in a patient followed up for 3 months are encouraging in treating patients having a high risk of RPE tear or bilateral neovascularization that would need bilateral intravitreal injections. However, medical cover, to identify and manage potential drug-related systemic adverse effects, must be provided by an oncologist accustomed to such treatments. We recommend a large trial with long-term follow-up to confirm our promising results and evaluate the occurrence of adverse effects associated with systemic bevacizumab.

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