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Adverse Events Associated with Intraocular Injection of Anti-VEGF(bevacizumab) in Retinal Vein Occlusion: A Case Report

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Abstract **Introduction:** Antiangiogenic agents are often administered for treatment of Branch Retinal Vein Occlusion (BRVO). Among them, Bevacizumab has noticeable antiangiogenic and antiedemigenic properties and possesses great capacity to penetrate the retinal tissue, particularly in pathological circumstances characterized by altered external or internal blood-retinal barrier.Bevacizumab has an optimal bio-efficacy based on inhibition of the activity of Vascular Endothelial Growth Factor (VEGF). Nonetheless, despite its efficacy, here we describe the adverse effects associated with intraocular injection of bevacizumab in a patient affected by retinal vein occlusion. **Case presentation:** We present a case report of an 11-year old Caucasian malesubject affected by BRVO in his left eye. The patient underwent an intra-vitreal (i.v.) injection of bevacizumab 100 (1.25 mg/0.05ml). After that, the patient was monitored over time through a series of analyses including Ocular Coherence Tomography, Fluorangiography, Bulbar Ultrasound, Angio MRI BCVA scores and Intra Ocular Pressure. **Results:** Immediately after the i.v. injection, the patient experienced a strong and relentless pain radiating from the left ocular orbit, caused by a serious and unexpected malignant glaucoma and phthisis bulbi. Furthermore, the patient did not show any sign of improvement in visual function in the follow-up and at last required an ophthalmic prosthesisas a result of a sub-atrophic and hypotonic eyeball. **Conclusion:** This case report suggests that i.v. injections of anti-VEGFs should be considered with caution when treating central and branch vein occlusion, and are not free of complications in certain clinical cases.

Keywords: *retinal vein and vascular occlusion, macular edema, intravitreal anti-VEGF, malignant glaucoma*

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1. Introduction

Branch Retinal Vein Occlusion (BRVO) is the most frequent vascular pathology after diabetic retinopathy, with an incidence of about 2.14/1000 per year in the population over 40 [1,2].This condition is characterized byretinal ischemia, neo-vascularization, intra-retinal sector haemorrhages and macular edema (ME). This pathology causesan immediate loss of visual acuity due to a series of physiopathological events, such asreduced capillary perfusion(with consequent retinal hypoxia) and an increased hydrostatic pressure resulting in haemorrhage and exudation of fluid [3]. So far, the preferred treatment modality isthe laser photo-coagulation, althoughnew therapies based on intra-vitreal (i.v.) administration of anti-vascular endothelial growth factor (VEGF) and cortisone have been more recently introduced [4,5,6].

VEGF is the biggest angiogenic stimulus responsible for the development of anomalous blood vessels in retinal vascular pathologies [7]. It has been demonstrated that intra-vitreal VEGF levels are significantly increased after central retinal vein occlusion, and, in case of ischemia, this increase may lead to loss of tight junctions, vascular leakage and ultimately edema [8]. Accordingly, nowadays it is recognized that the use of anti-VEGFs may improve the state of retinal micro-circulation [9].

Bevacizumab, a full-length humanized monoclonal antibody, is a VEGF inhibitor initially used in the treatment of metastatic colon-rectal cancer [10], and successively adopted to treat neovascular retinaldiseases [11]. The mechanism of action of bevacizumab is different from that of other anti-angiogenic compounds. While pegaptanib and ranibizumab penetrate the retina and reach the choroid, bevacizumab penetrates directly into the choroid, thus closing anomalous blood vessels [12]. This medication (given i.v.) is currently in use for the treatment

of different pathologies, such as Choroidal Neo Vascularization (CNV) caused by Age related Macular degeneration (AMD) [13,14], central retinal vein occlusion (CVO) [15], Diabetic Macular Edema (DME) and proliferative diabetic retinopathy (PDR) [2]. Here we present a case of ocular complications in a patient affected by retinal vein occlusion and treated with intraocular injection of bevacizumab.

2. Case Presentation

In November 2013, a 11-years old patient with a 2-months history of blurred and distorted vision in left eye (LE) was admitted to our observation unit. Amsler grid test showed metamorphopsia in the LE and normal findings in the right eye (RE).The examination of the anterior segment was normal, and intra-ocular pressure (IOP) was 16mmHg in both eyes. Best corrected visual acuity(BCVA) was 20/50 in the LE and 20/20 in the RE.

Biomicroscopic examination of the ocular fundus revealed acentral retinal vein occlusion with macular edema, confirmed by optical coherence tomography (OCT), an alteration of the chorio-capillary barrier and epithelial pigment, and increased foveal thickness (FT) 480 micron (Figure 1).

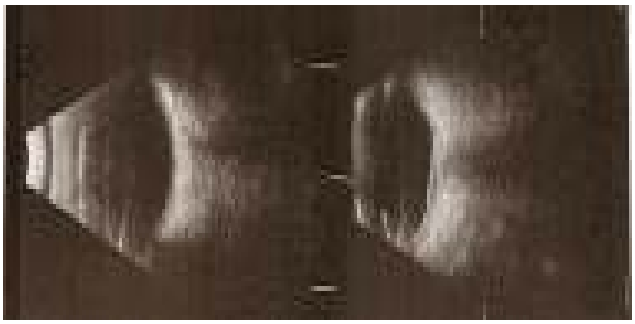

Figure 1. Bulbar ultrasonograhy: Vitreous dis-homogeneity left eye (LE) > right eye (RE).

LE: liquid type alterations of the retinal profile in the posterior pole with involvement of the macula and optic disc. Edema of the optic nerve sheath.

A bulbar ultrasonograhy revealed a vitreous dyshomogeneity in the LE, with liquid type alterations of the retinal profile in the posterior pole, with involvement of the macula and optic disc. An edema of the optic nerve sheath was present, with no evidence for expansive pathologies at the orbital site.

Fluorescein angiography (FA) showed a picture of BRVO of ischemic- hemorrhagic type, with hyper-fluorescence of the optic disc in the LE (Figure 2, Figure 3).

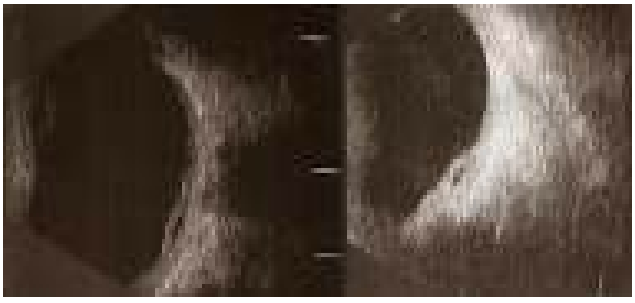

Figure 2. Ultrasonograhy orbital: Non evident expansive pathologies at the orbital site. Para-nasal sinuses well evident. RE: retina always on plane and acoustic wave of the optic nerve within standard limits

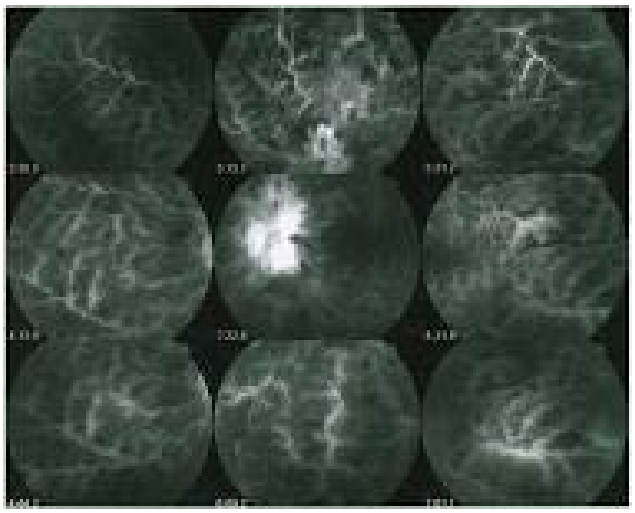

Figure 3. Fluorescein angiography (FA): BRVO of the ischemic-hemorrhagic type. Hyper-fluorescence of the optic disc in the left eye (LE) and no alterations of the hemo-retinal barrier (HRB) in right eye (RE)

The RE did not present alterations of the blood-retinal barrier (BRB), with retina always on plane and acoustic wave of the optic nerve within standards (Figure 2, Figure 3).

Routine Blood tests showed the following altered values: alkaline phosphatase (283 IU/L, range 42-121 IU/L); anisocytosis (RDW 18.5%, range 10-16%); hyperchromia and microcytosis (MCV 65 fl, range 80-100; MCH 19.4 pg, range 26-34 pg),and neutropenia (NEU% 43.2, range 50-80%). Immunological tests, anti-viral antibodies, anti-Toxoplasma, and VDRL were all negative.

2.1. Neurological Examination

Brain and Angio MRI showed a normal appearance of internal carotid arteries and their principal intracranial afferents. There were no evident alterations in the vertebro-basilar region and a representation of the principal intra-cranial venous branches with normal limits. Fearing a possible thrombosis or onset of a carotid dural cavernous fistola, an arteriography was proposed to the patient's parents, but they did not give consent to this diagnostic procedure.

2.2. Initial Treatment

With informed consent, the patient was initially treated with a symptomatic general therapy consisting of seleparine (2850UI/0.3ml 2 fl. subcutaneously), Prednisolone (25 mg/day, os), acetazolamide (250 mg/day, os) specifically indicated in the treatment ocular hypertonus, gastric protectors (150 mg/day, os) and a food supplement (one tablet/day).

2.3. Bevacizumab Intravitreal Injection and Follow-up Complications

Not noticing any improvement in child's condition, the parents decided to take him to another hospital where he was subjected to intravitreal injection (i.v.) of bevacizumab 100 (1.25mg/0.05ml) tohis LE.

Few hours after the injection, the patient complainedan intense pain in the LE and was brought again to our attention. His IOPin his LE was now 64mmHg. The patient was immediately treated with endovenous mannitol

(250mg×2) (drop infusion), acetazolamide (250 mg os; three tablet/ day) and topical atropine. To reduce pain and congestion, steroids, timolol drops, and carbonic anhydrase inhibitors were also administered.

After a week, the pain was still relentless and unbearable and his IOP was 52mmHg. Thus, to manage the painan elastomeric pump was implanted and used to administer ketorolac, initiallyat a dose of 90mg and successively 48 mg (2 mg/h × 24h).

Moreover, 20 applications of cyclo photocoagulation with YAG- laser free running mode (5.5 J)in the inferior section of the eye-ball (2.5 mm from the limbus) were given. During this time, haloperidol (1 mg)and orphenadrine hydrochloride(50 mg)were prescribed to the patient because of his altered psycho-physical condition.

A new bulbar ultrasonography was repeated in the LE. Amarked dyshomogeneity vitreous inflammation was found, together with signs of retinal detachment (RD)of papillary origin and involving the macula of all the temporal sector of the eye (Figure 4). FAG also showed evidence of peri-papillary hemorrhage in RE (Figure 5, Figure 6).

Figure 4. Bulbar ultrasonograhy at 20 days from the acute events in the LE: Marked dis-homogeneity vitreous inflammation. Altered retinal profile for retinal detachment (RD) of papillary origin and involving the macula of all temporal sectors of the eye

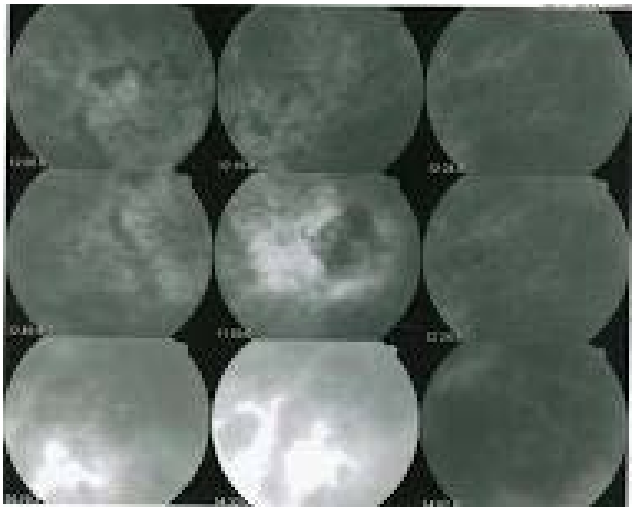

Figure 5. FAG showed evidence of peri-papillary hemorrhage in right eye (RE)

After 1 and 2 months from the acute event, LE visual acuity (AV) had markedly worsened to hand motion (HM). Rubeosis iridis was present at objective examination and IOP was 44 mmHg. A diffuse edema retinal was present and barely investigable because of an endovitreal hemorrhage. This edema was principally located in the posterior pole of the fundus, which was lifted at ophthalmoscopic examination. Bulbar Ultrasound (Figure 7) produced pathological echoes in the vitreal chamber, attributable to endovitreal hemorrhage with a posterior detachment of the vitreous membranes. The retinal alteration in the posterior pole was associated to organized exudation and retinal detachment.

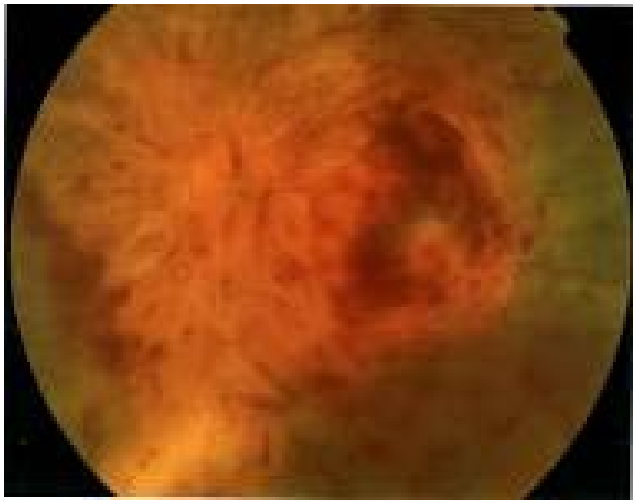

Figure 6. FAG showed evidence of peri-papillary hemorrhage in the right eye (RE)

Figure 7. Bulbar ultrasonograhy: Pathological echoes in the vitreal chamber attributable to endovitreal hemorrhage with a posterior detachment of the vitreous membranes, particularly in the superior section

Four months after the acute event, LE IOP progressively diminished to 23 mmHg with a consequent reduction of pain. Nonetheless, the patient showed athalamia and massive neo-vascularization, possibly evolving in a bulbar phthisis.

After one year, the patient required an ocular prosthesis, as a result of a subatrophy and hypotonic eyeball without signs of flogosis.

3. Discussion

Macular edema (ME) is the most frequent cause of loss of vision [1,2,3] and is generally treated with either focal photocoagulation [4,5] or, more recently, with i.v. triamcinolone [6]. However, laser photocoagulation causes an irreversible destruction of para-central retinal tissue and thus new treatment modalities have been developed.

Anti-angiogenic drugs, like corticosteroids, ranibizumab, pegaptanib and bevacizumab, represent new treatment options for ME without causing tissue damage [9,16,17]. In particular, antiangiogenic drugs may be useful for reducing both edema and neo-vascularization in occlusive pathologies [9,12,15]. Among them, bevacizumab,

administered i.v., has become the reference treatment option for the cure of ocular occlusive pathologies [16,18]. When compared to the traditional laser therapy, bevacizumab has been shown to induce comparable and significant improvements in patients affected by ME secondary to branch retinal vein occlusion (BRVO), both with chronic [19] or acute i.v. administration [20,21].

In case of BVRO, the optimal treatment strategy is still matter of debate. Natarajan (22) states that, in the majority of cases of Central Vein Occlusion (CVO), the disease may undergo to spontaneous regression after 3 months. However, in the CVO case reported here, no improvement in BCVA and ME was observed. Therefore, after 20 days of retinal vein occlusion (RVO), the patient underwent a fluorangiography (FAG) in order to establish the more appropriated therapeutic approach [16]. Photocoagulation or laser therapy could not be adopted because ME was such extensive to limit their efficacy [18,24]. Thus, as the patient did not show any improvement in his visual function during time, his parents decided to subject him to i.v. injections of bevacizumab in another health institute. The bevacizumab i.v. injection did not improve his retinal condition, and on the contrary provoked a greater dilation and a entanglement of the retinal veins, also evidenced by the FAG [12].

The reason for this failure is not clear. Bevacizumab is a drug inhibiting the development of neovascularization by blocking the molecular pathways of VEGFs and on their pro-angiogenic input [11,12]. Although this pharmacological action has been shown to be beneficial in case of ocular occlusive pathologies, the physiopathological mechanisms underlying RVO [23,24] and the role of VEGFs in ME [25] remain to be determined. Experimental studies suggest that VEGFs may also play a protective role in the hemo-dynamics of the retina and even a direct retinal neuroprotective role, particularly in hypoxic conditions [18,25]. In a recent review by Manousaridis and Talks [26], it is evidenced that in case of venous occlusion VEGFs promote the restoration of venous flow through the formation of blood vessels and blood perfusion in retinal unperfused areas, thus preventing ischemic lesions in the retina [9,25]. In addition, studies performed in primates have shown that anti-VEGF treatment reduces chorio-capillary fenestrations of retinal endothelial cells, increasing the ischemic damage in the internal retina [3].

These studies suggest that the blockade of VEGF action in cases of significant is chaemia at baseline may be detrimental to the retinal circulation. Supporting this notion, it has been demonstrated that repeated injections of bevacizumab may cause harmful effects on neuronal viability of retinal ganglion cells in rats [27]. In humans, retinal detachment (retinal pigment epithelium RPE) has been reported in two patients after repeated bevacizumab injections [24] while in a study of 707 patients both systemic and local complications were reported, although in minimal percentages [17]. Systemic complications included cerebral infarct, elevated systolic pressure, skin rashes and irregular periods while the most commonlocal complications were corneal abrasions, lesions of the crystalline, inflammation, RPE detachment, and loss of vision [22]. These and other data have led to the suggestion that maintaining a normal balance between antiangiogenic and proangiogenic VEGFs (VEGF 165/VEGF165b) would be a more suitable approach, instead of only targeting proangiogenic VEGFs [7,18,25,28]. However, it should be noted that in the present case report bevacizumab injection was performed in another health institute and consequently we lack necessary information on the accuracy of the procedure adopted or other possible complications risen during that period.

4. Conclusions

In conclusion, in the case report just presented, the decision to use i.v. bevacizumab injections did not prove to be the best choice as the results were dramatic. Ultimately, the patient was forced to adopt an ocular prosthesis because of the resultant phthisis. Although anti-VEGF agents are used in the management of ME with retinal vein occlusion [25,26,29], we believe that these therapies should be considered with caution because of the insufficient knowledge of the physiopathological mechanisms by which they act in retinal occlusive pathologies. In addition, further studies are necessary to establish the optimal dose range in young patients, as compared to adults.

List of abbreviations

Best corrected visual acuity(BCVA), Branch Retinal Vein Occlusion (BRVO), blood-retinal barrier (BRB), Choroidal NeoVascularization (CNV), central retinal vein occlusion to (CVO), Diabetic Macular Edema (DME), Fluorescein angiography (FA), hemo-retinal barrier (HRB), intraocular pressure (IOP), intra-vitreal (i.v.), Left eye (LE), Right eye (RE), macular edema (ME), optical coherence tomography (OCT), proliferative diabetic retinopathy (PDR), Retinal detachment (RD), Vascular Endothelial Growth Factor (VEGF),visual acuity (AV).

Consent

"Written informed consent was obtained from the parents of the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal."

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Author Contributions

Conceived and designed the experiments: EP, FP. CDP, Analyzed the data: EP, FP, PT. CDP, MA. Wrote the first draft of the manuscript: FP. EP, CDP. Contributed to the writing of the manuscript: FP, PT, CDP, MA. FRP. Agree with manuscript results and conclusions: EP, FP, PT, CDP, FRP. Jointly developed the structure and arguments for the paper: EP, FP, PT, AM, CDP, FRP. AB. Made critical

revisions and approved final version: EP, FP, PT, MA, CDP, AB. FRP.

Statement of Competing Interests

The authors declare that they have no competing interests.

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