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Case Report

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Secondary Adverse Effects of Anti- Vascular Endothelial Growth Factor Therapy in Choroidal Circulation Case Report

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Abstract

Recent research has shown that abnormal production of vascular endothelial growth factor (VEGF) is an often finding in ocular pathologies involving neovascularization. The regulating factors that set the production of VEGF are not well understood, and only the presence of hypoxia in tissues is the most studied factor. But the regulation of oxygen levels in tissues is also not well elucidated, so therapies in this regard were not efficient. The availability of technology that allows to manufacture antibodies to the measure, allowed to design antibodies Anti VEGF. However, its therapeutic effects are far from what is expected because more is unknown than is known about VEGF. Therefore, its side effects as well as adverse effects are frequent, and even exceed its positive effects. The antiangiogenic effect of anti-VEGF antibodies is not selective, that is, it does not distinguish between normal vessels and neo-forming vessels. In this paper we report the adverse effects on the blood vessels of retinal and choroidal tissue of the intraocular application of anti-VEGF antibodies, and its impact on the form and function of these tissues.

Background

Over the past 20 years new agents targeting VEGF have become commercially available for intraocular use [1]. ("Anti-vascular endothelial growth factor therapy for ocular ...") Different clinical trials showed that anti VEGF therapy prevented moderate vision loss in neovascular age related macular degeneration. Smaller case series have shown that anti-VEGF can regress retinal, iris and disc neovascularization. ("Anti-vascular endothelial growth factor therapy for ocular ...").

Due to Age-related macular degeneration (AMD) is the most common cause of uncorrectable severe vision loss in people aged 55 years and older in the developed world, it has been the most treated disease with anti-VEGF [2]. "Choroidal neovascularization (CNV) secondary to AMD accounts for most cases of AMD-related severe vision loss." ("Anti-vascular endothelial growth factor for neovascular ...") Intra-Vitreous injection of anti-vascular endothelial growth factor (anti-VEGF) agents aim to block the growth of abnormal blood vessels in the eye to prevent vision loss and, in rare instances, to improve vision, even in trials conducted or sponsored by pharmaceutical companies [3].

In spite that reduction in central retinal thickness is often reported, it is not mean better final visual acuity. Ocular inflammation and increased intraocular pressure (IOP) after intravitreal injection were the most often reported serious ocular adverse events. ("Anti-vascular endothelial growth factor for neovascular ...") Endophthalmitis (a serious complication) is reported in less than 1% of anti-VEGF-treated trial participants and in no cases among control groups.

It is striking that Investigators rarely measured and reported data on visual function, quality of life, or economic outcomes. Available information on the adverse effects of each medication apparently does not suggest a higher incidence of potentially vision-threatening or life-threating complications with intravitreous injection of anti-VEGF agents compared with control interventions; perhaps, clinical trial sample sizes were not sufficient to estimate differences in rare safety outcomes. ("Anti-vascular endothelial growth factor for neovascular ...").

Injection frequency varies among practitioners, which underscores the need to characterize an optimized approach to neovascular Age-

related macular degeneration (nAMD) management. ("Comparing different injection frequencies for neovascular ...")

Introduction

The treatment of ocular neovascular diseases is expected to be revolutionized by intravitreal therapies targeting vascular endothelial growth factor (VEGF). The agents that are approved for treating neovascular age-related macular degeneration and are being applied for other retinal conditions although its use is off label. ("Systemic and ocular safety of intravitreal anti-VEGF ...").

Because VEGF takes part in a wide variety of physiologic processes, the ocular and systemic safety of anti-VEGF agents is of paramount concern [4]. ("Systemic and ocular safety of intravitreal anti-VEGF ...") The principal ocular adverse event detected in clinical trials was a low frequency of ocular inflammation, and systemic adverse events included a slightly elevated risk of non-ocular (brain) hemorrhage and stroke. Safety data from meticulously designed randomized controlled trials for anti-VEGF are not available.

In diabetic retinopathy patients, especially those with diabetic macular edema unresponsible o partially responsible to intravitreal anti-VEGF application, is so frequent that options have been looked for, such as subthreshold nondamaging retinal laser therapy (NRT); but it should be assessed in more detail with prospective controlled studies [5].

Case Report

Male patient, date of birth: 07/02/1950; with diabetes mellitus since 2001, currently treated with 14 I.U. if insulin every 24 hours.

He first went to consultation on 11/14/2016, and the diagnoses at that time were diabetic neuropathy (paralysis of the VI right pair), and pre-macular gliosis of the right eye.

On that occasion, the patient was treated with QIAPI 1, sublingual gout, at the dose of three drops every two hours during the day, which improved substantially the paralysis of the right external rectum and the pre-macular gliosis stopped.

Subsequently, on 03/06/2018, the patient returned reporting low vision of the right eye, the clinical photographs of that consultation are shown below: (Figures 1-4)

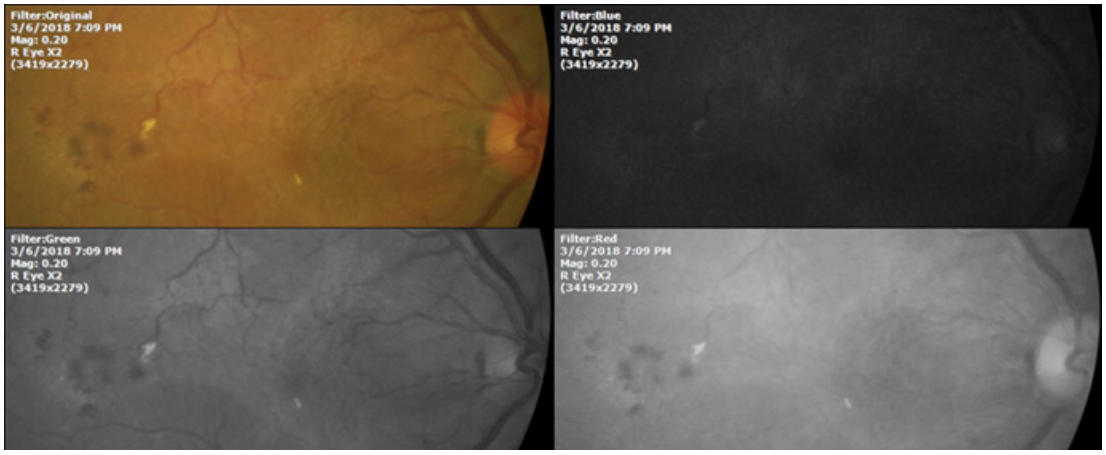

Figure 1: Right eye. The presence of dot hemorrhages, and gliosis on macular area.

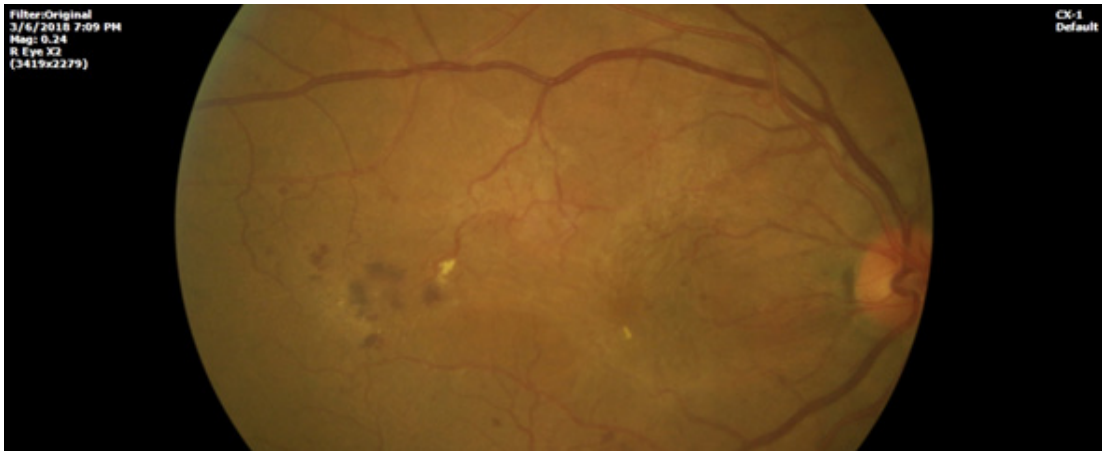

Figure 1: Right eye. Blood vessels diffuse alterations, such as vasodilation, tortuosity, increase tortuosity, and the vascular wall reflection of arterioles is more than one third.

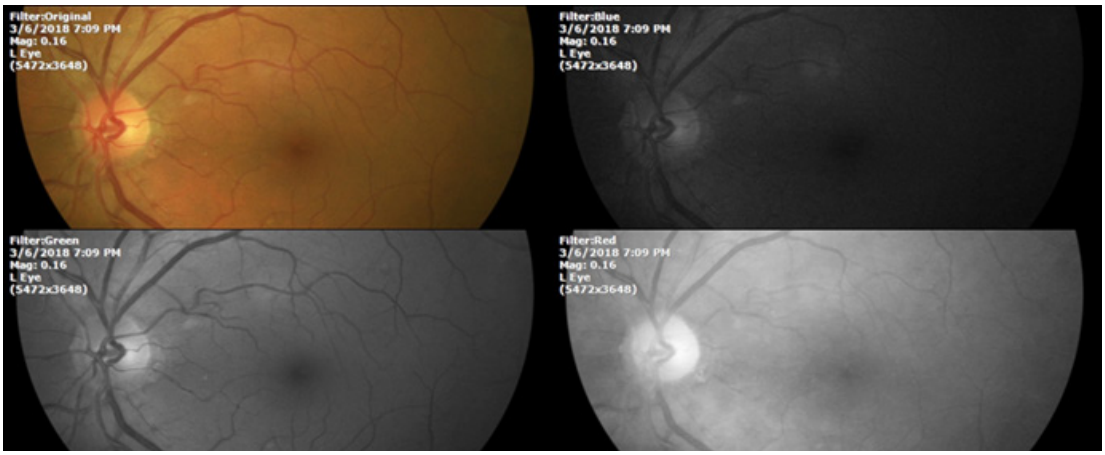

Figure 3: Left eye. The vascular characteristics are relatively well preserved.

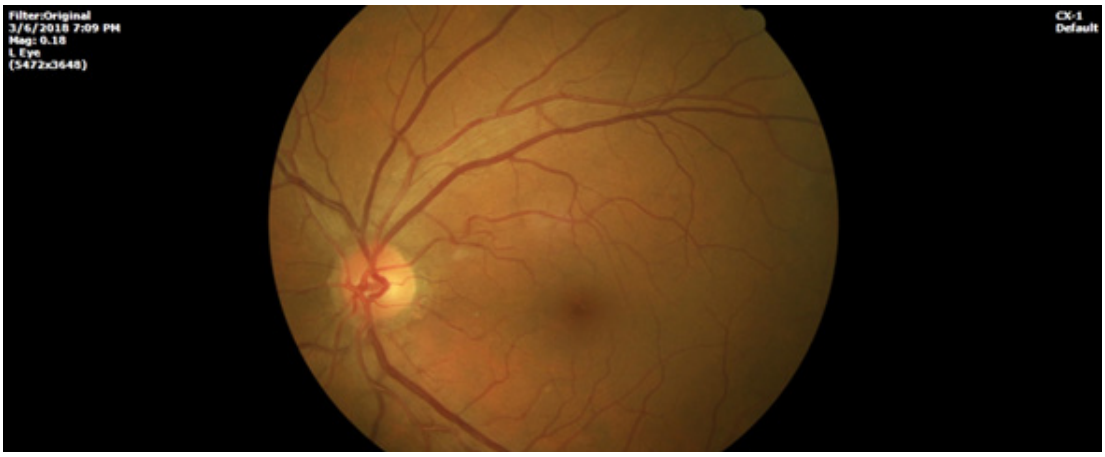

Figure 4: Left eye. There are two small patches of gliotic activity.

On 06/05/2018, the patient returned referring that the improvement was going slowly in spite to keep the treatment continuously. The photographs of that consultation are shown below (Figures 5-8).

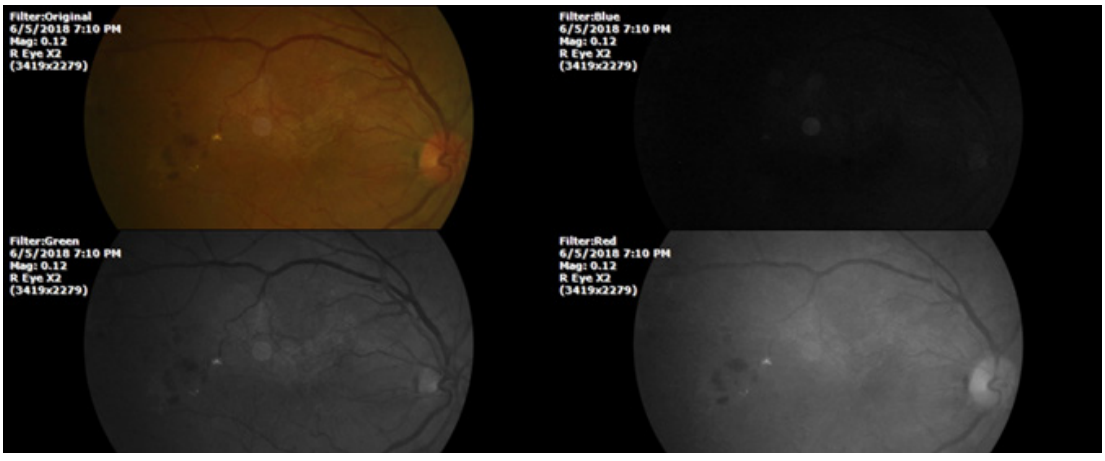

Figure 5: Right eye. The dot hemorrhages diminished, and macular area is less affected by gliotic activity.

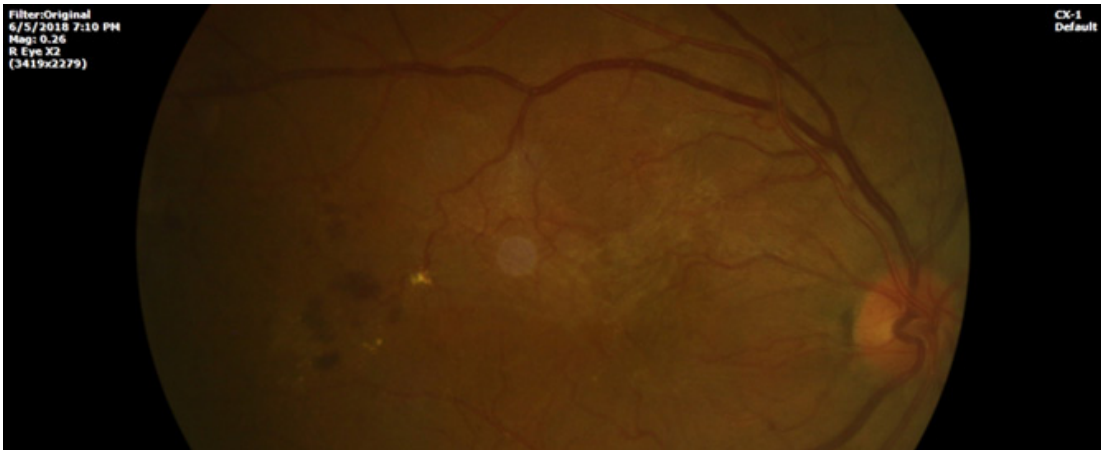

Figure 5: Right eye. Tortuosity of blood vessels is significantly less than the first consultation. The arteriolar constriction saw initially, improved also.

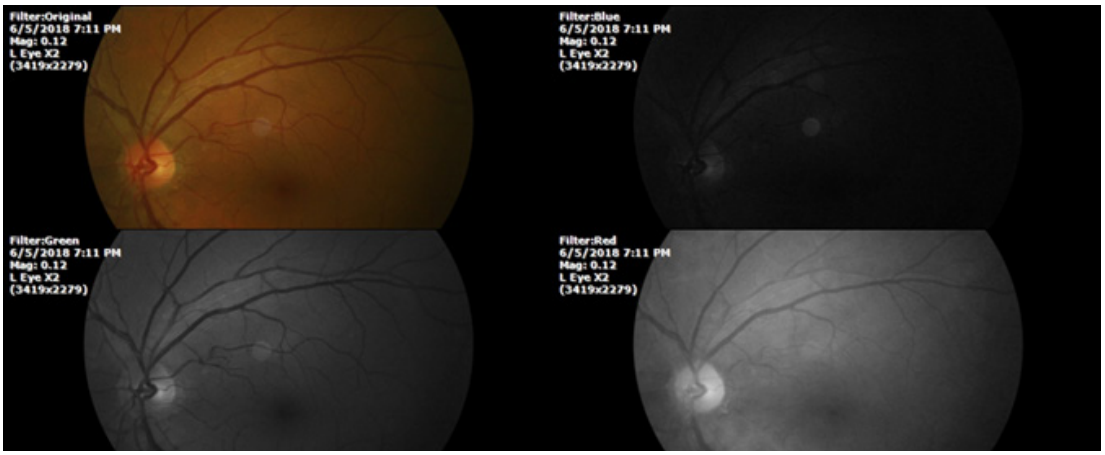

Figure 6: Left eye. The characteristics of blood vessels, macula, optic nerve, and vitreous is preserved.

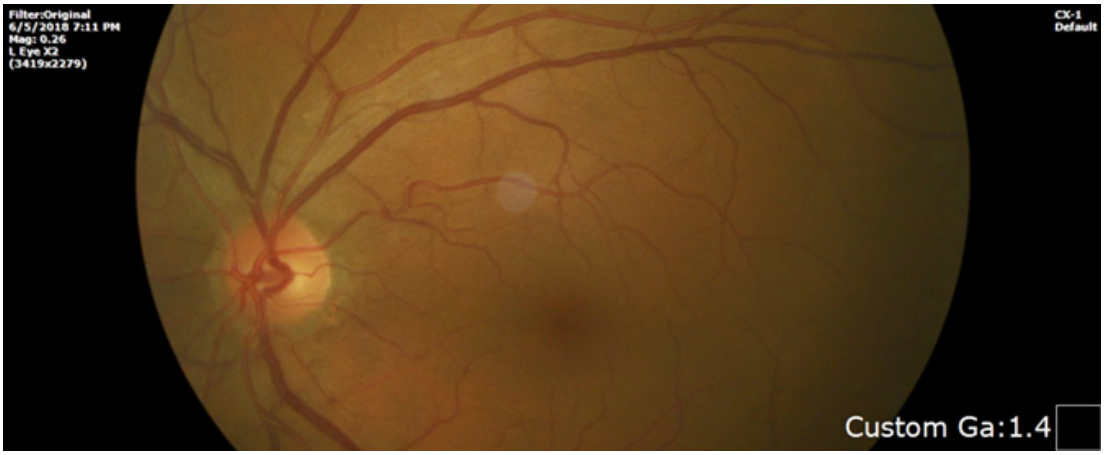

Figure 8: Left eye. The small patches of gliotic activity disappeared.

The next time the patient returned to consultation, was 05/13/2020, referring that in 2019, an ophthalmologist suggested the intravitreal application of anti VEGF in right eye. The patient uses constantly QIAPI 1™ sublingual drops.

The photographs taken on that occasion (05/13/2020) are shown below: Figure 9-12)

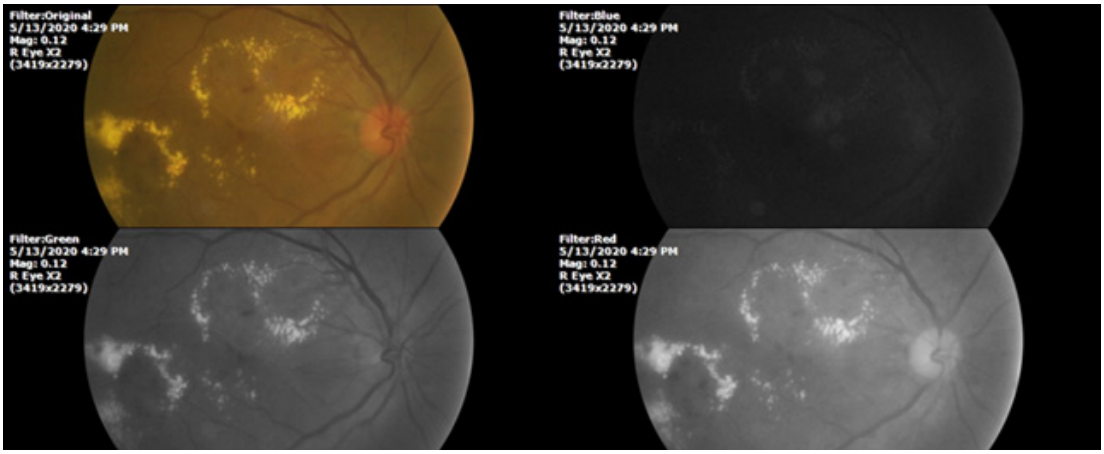

Figure 9: Right eye. Appearance of hard exudates organized around microvascular retinal complex, after intra-vitreous application of anti VEGF therapy.

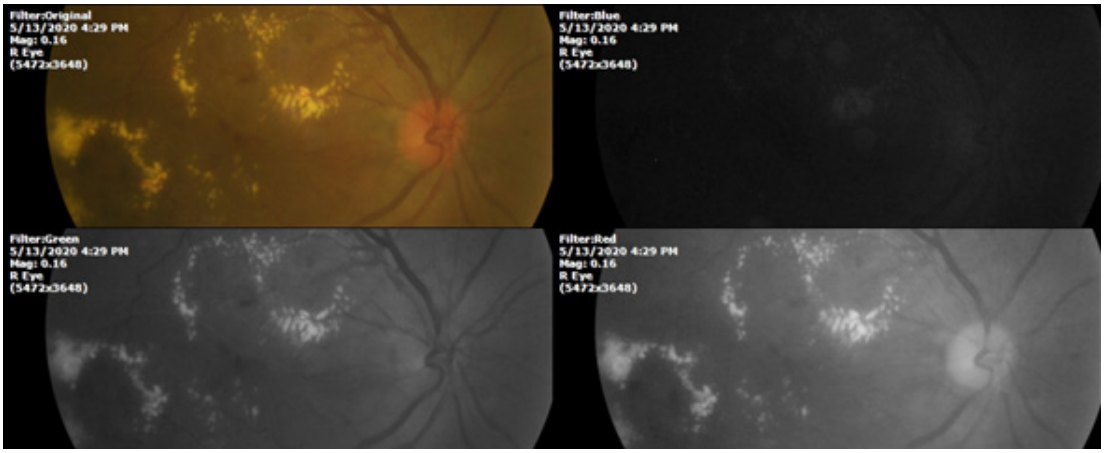

Figure 10: Right eye. The distribution of hard exudates around microvascular retinal complex, means that smallest capillaries are mainly affected for anti-VEGF therapy.

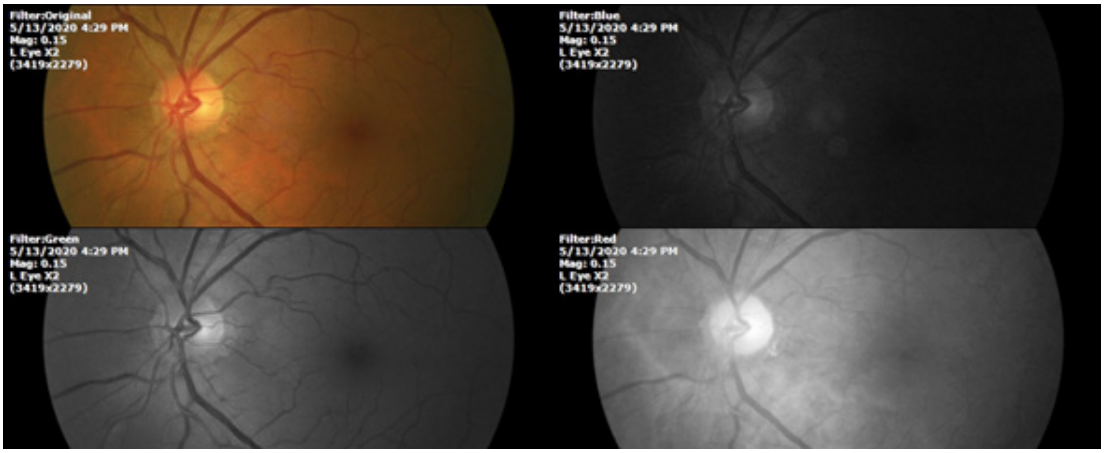

Figure 11: Left eye. The anti VEGF therapy was applied only in right eye, thereby, the left eye had not changes suggesting damage.

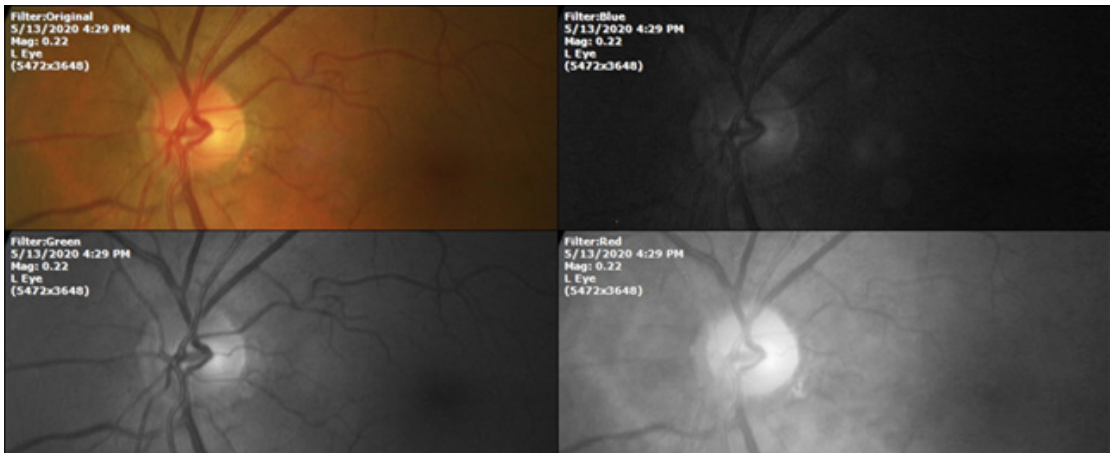

Figure 12: Left eye. The general appearance of the optic nerve, blood vessels, and macular area without notable change.

The patient was advised not to inject anymore and to only to continue with the treatment of QIAPI 1, sublingual drops, three drops every hour.

However, during the last review, conducted on 02/08/2022, the patient reported that due to family pressures, he accepted again the intravitreal injection of anti-VEGF, but QIAPI 1™ was continuously used. The fundus photographs taken on 02/08/2022 are shown below: (Figures 13-22).

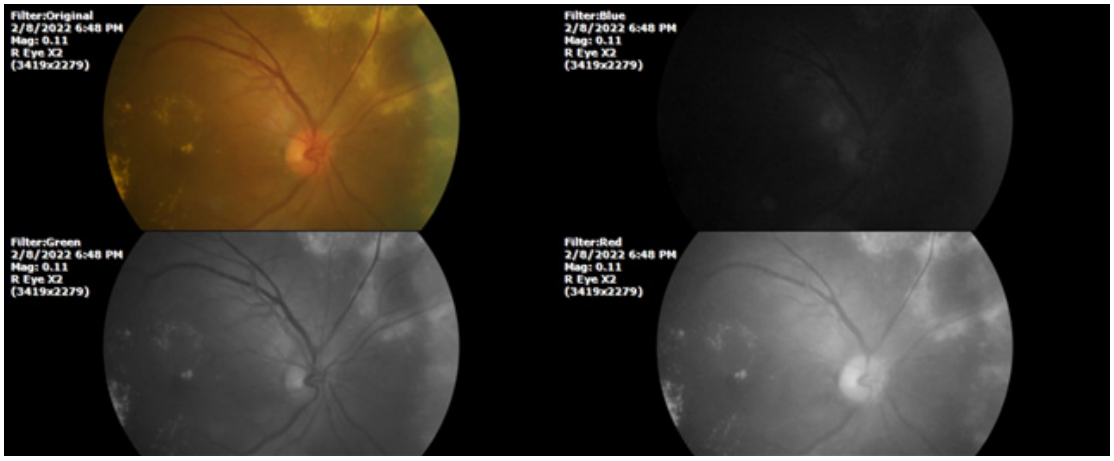

Figure 13: Right eye. After the second treatment of anti VEGF therapy, new areas of hard exudates, of deepest location, now are seen in nasal region, and seems are due to choroidal blood vessels affectation.

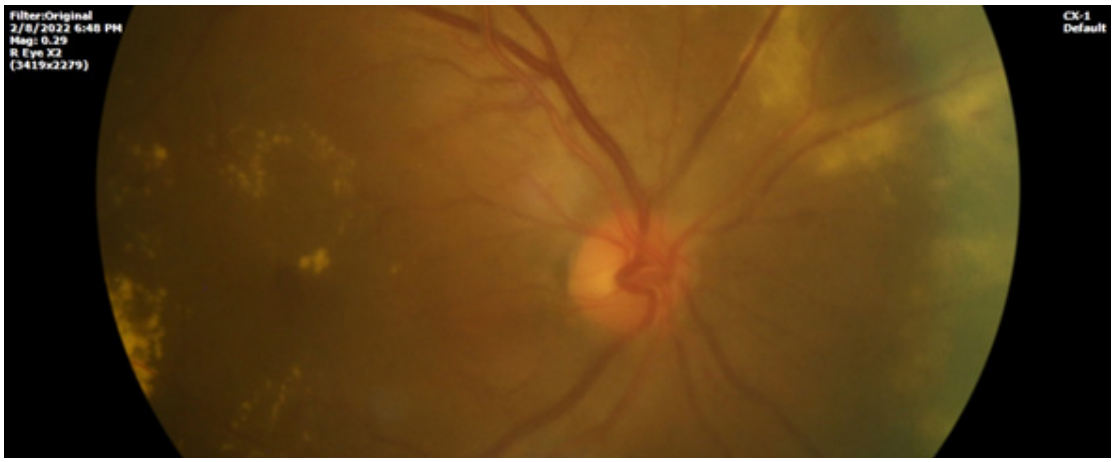

Figure 14: Right eye. After second treatment of anti VEGF therapy, the new hard exudates are now distributed in nasal and superior area.

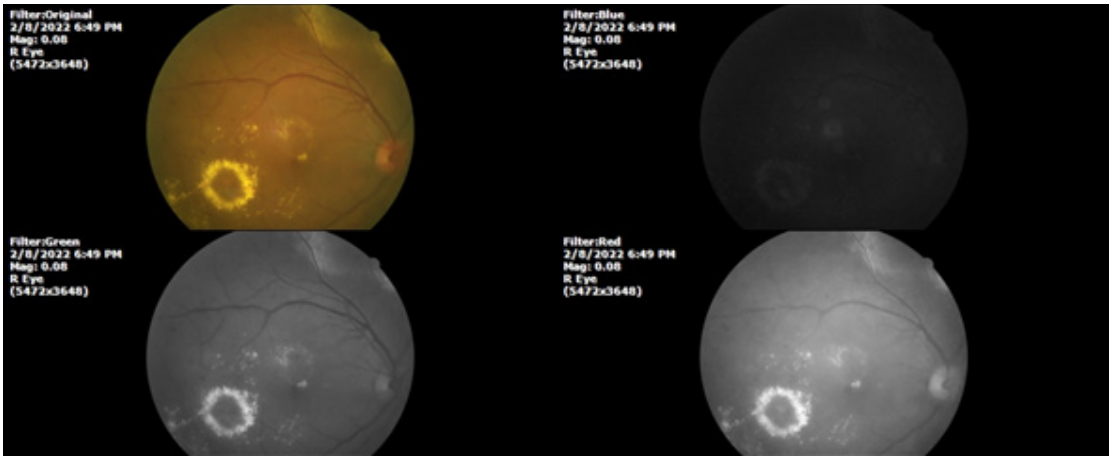

Figure 15: Right eye. The exudates that appear after first treatment with anti VEGF treatment that disappear with QIAPI 1™ sublingual drops treatments, close to macular area, still show improvement, except by the exudate of temporal region, now denser.

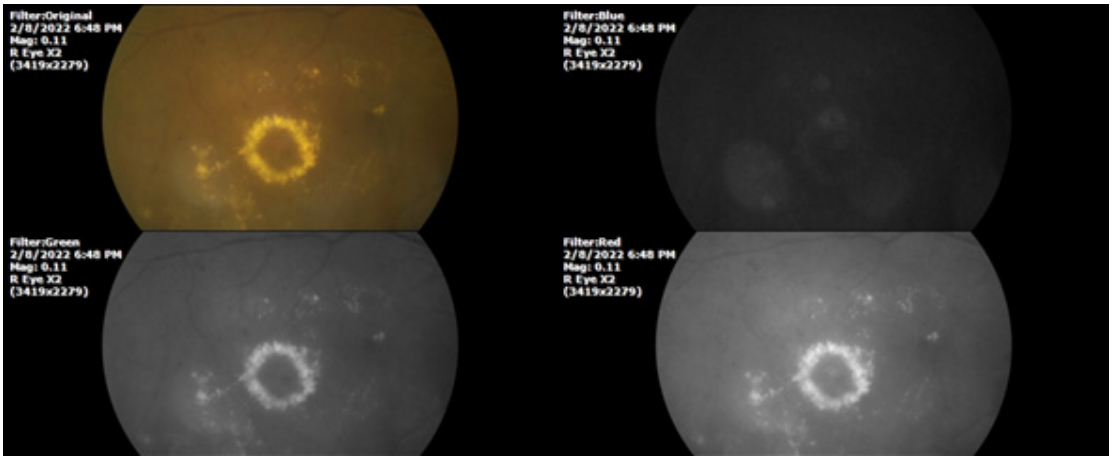

Figure 16: Right eye. This exudate appears after the first treatment of anti VEGF therapy. Other exudates improved significantly, and after second treatment of anti VEGF therapy, applied only to right eye, possibly deteriorated this specific area.

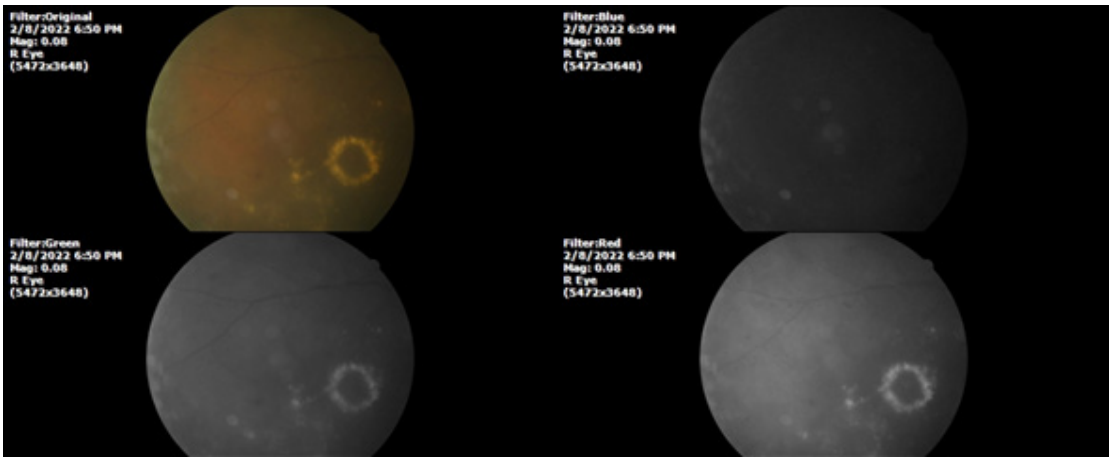

Figure 17: Right eye. The farthest temporal area shows subtle circle-like formation of exudates.

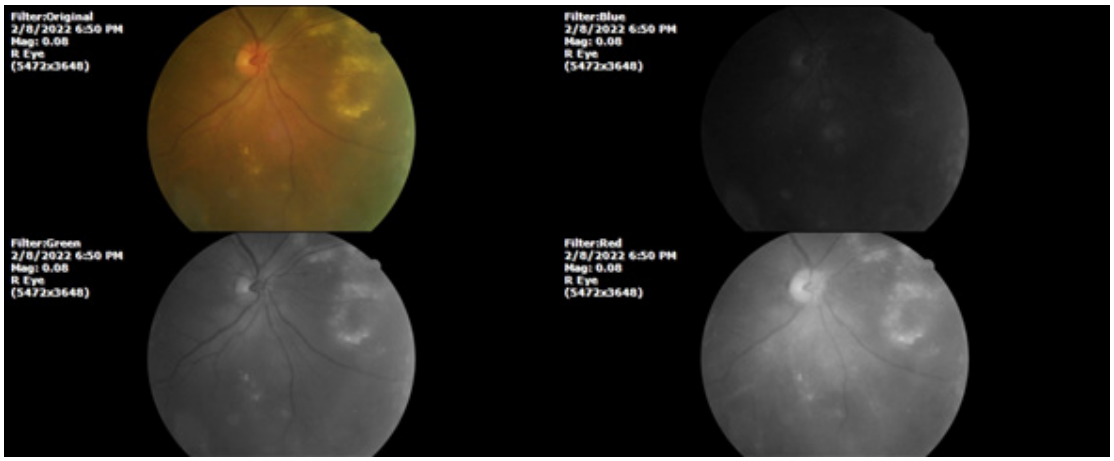

Figure 18: Right eye. The nasal region, in the inferior part, shows distinct levels of affectation.

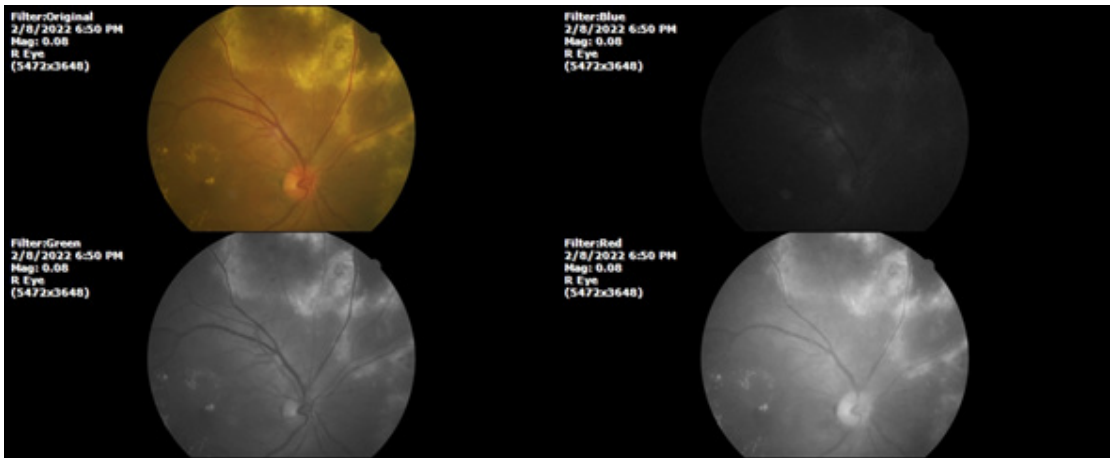

Figure 19: Right eye. Right eye. The nasal- temporal region distally, shown the largest areas of exudates formation after the second anti VEGF treatment.

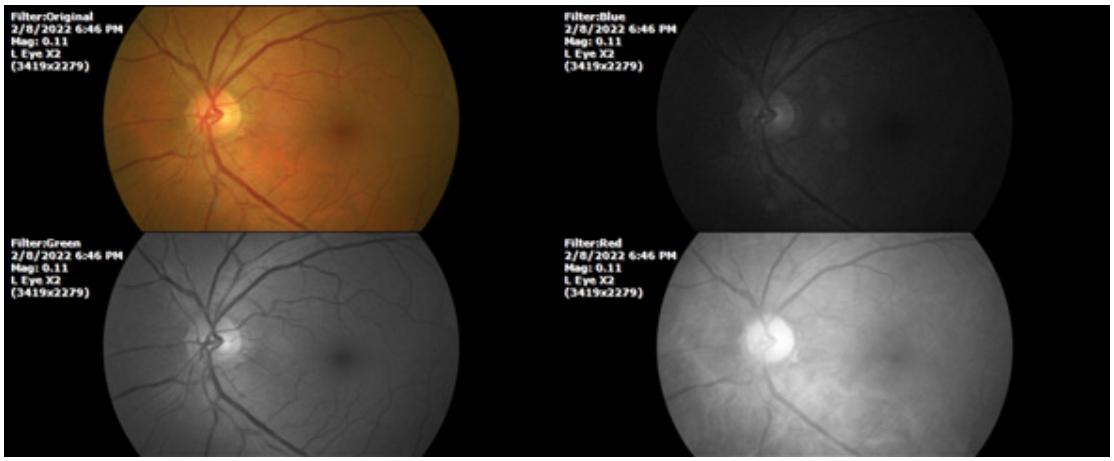

Figure 20: Left eye. This eye apparently was not affected by the treatment of the right eye.

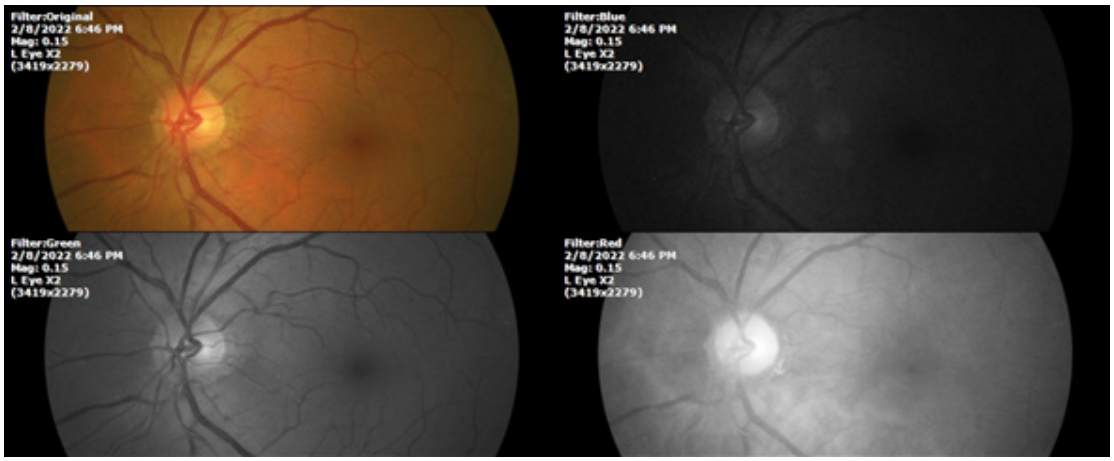

Figure 21: Left eye. The macular area, the optic disc, blood vessels, and retinal tissue seems in undamaged shape.

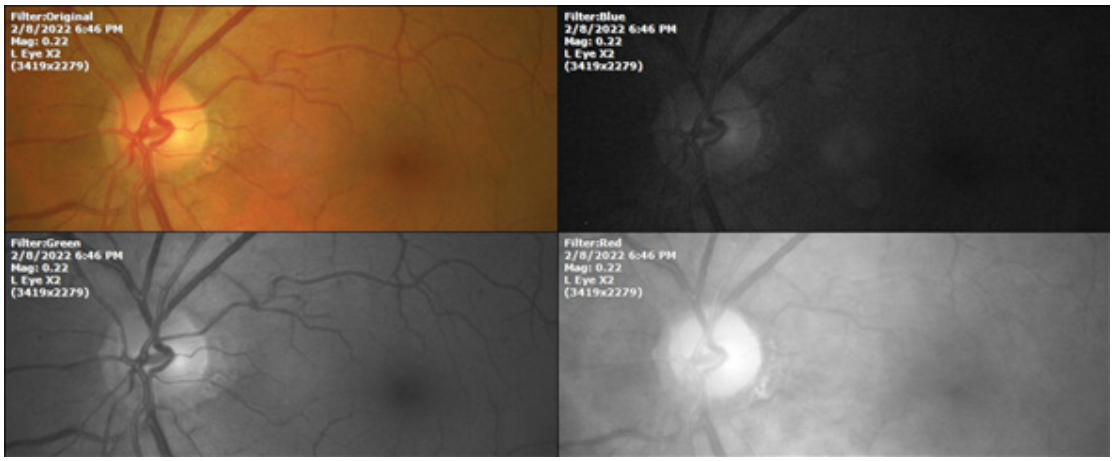

Figure 22: Left eye. The blood vessels of the optic disc as the macular area are unremarkable.

The addition of anti VEGF therapy to the right eye worsening instead of improving the anatomical alterations and function problems of retinal and choroidal tissues, including blood vessels. Unfortunately, this is the rule more than the exception.

Anti VEGF therapy closes -indiscriminately- normal and abnormal blood vessels. And its effects are not during a brief time. Studies with therapeutic VEGF and anti VEGF administration resulted in quite variable results depending on the route and time point of delivery [6].

Tissue remodeling is a highly dynamic process, which means energy expenditure and involves close and finely tune interactions between neuronal, glial, and vascular cells. These cells release various trophic factors through which they mutually influence each other, thus creating a permissive environment in which successful tissue recovery may take place [7].

Thereby, QIAPI 1™ has better therapeutic effect than anti VEGF therapy, because its effect on energy generation and distribution, upregulating the turnover rate of water dissociation impact extensively the biology of retinal tissue, one of the most demanding metabolic tissues.

Comment

We based our therapeutic strategies on the unsuspected intrinsic capacity of a handful of molecules, normally present in human body, to transform the power of sunshine into chemical energy through the dissociation of water molecules [8].

This process -water dissociation- is astonishingly exact and has been since beginning of times. However, this accuracy is impaired by polluted air, contaminated water, pesticides, herbicides, fertilizers, metals, plastics, solvents, industrial waste, residual waters, alcohol, etc.

Retinal tissues, blood vessels, and in general terms, any tissue should disorganize when water dissociation -the very first reaction of life- is perturbed and thereafter, the logic of the biochemical process that mold life tend to chaos and eventually any disease could be manifested.

A considerable number of cytokines produced in the eye have been suggested to play a role in the pathogenesis and progression of diabetic macular oedema (DMO) [9]. VEGF causes conformational alterations, such as phosphorylation and changes in protein content in the tight junctions of retinal vascular endothelial cells, which play a role in the increase in vascular permeability [10, 11].

The finding that aqueous level of VEGF was significantly correlated with its vitreous level means that VEGF is highly soluble and/or is secreted by different cellular lines [12].

It is a key point that the expression of VEGF is induced by hypoxia in retinal cells at least by two things: 1) Higher levels of oxygen is the best anti-angiogenic factor and 2) Oxygen in tissues does not come from atmospheric air instead come from water dissociation [13, 14].

Therefore, the overproduction of Vascular Endothelial Growth Factor (VEGF) is not the basis of the histopathological changes in diabetic retinopathy, instead is the impairment of the very first reaction of life, this is the water dissociation.

Life is characterized by an incessant interact with the surroundings to get energy. Supposedly, human beings obtain energy through meals. Theoretically, our cells "burnt" glucose to release energy, however, if glucose were source of energy, diabetics should fly.

Glucose is source of carbon chains only, and due to our body knows it since the beginning of time, glucose makes up the universal building block by which our body tissues and cells synthesize 99 % of biomolecules that mold us [15]. However, glucose cannot supply the energy that its own metabolism requires.

Thereby, glucose is source of biomass, and our body takes the energy necessary to make the biochemical changes at glucose from sunlight, after transforming it into chemical energy dissociating the water molecule, like the plants.

The splitting of the molecule of water is a highly endergonic reaction, this is: requires a huge amount of energy. In the laboratory, it is necessary to heat water at 2000 ° Celsius. But our body and plants make the reaction at room temperature.

So, the hypoxic retina is due to an impaired turnover rate of water dissociation, for instance: polluted air, contaminated water, and multiple agrochemicals in food, alcohol, exposure -chronic or acute- to industrial waste, and similar pollutants. And the abnormal upregulated level of VEGF is a consequence of the impairment of water dissociation, and not the causal factor. Therefore, the anti-VEGF therapy has a less than modest results and it's full of secondary effects [16].

Any hypoxic tissue means that the dissociation of water molecule is impoverished. In other words, the generation and distribution of energy is compromised and the myriad of biochemical processes that lead to life should not happen in the highly ordered way that occur in a healthy tissue.

Remember that the main product of water dissociation is hydrogen because hydrogen is the main carrier of energy in the whole universe, therefore, our body cannot be different. Oxygen only is byproduct characterized by its high toxicity.

Retinal edema, and choroidal neovascularization are manifestations of an extended disorganization, this is: a general failure of innumerable systems at the same time, which is characteristic -in any system- of an energy problem.

Conclusion

The discovery of a handful of body molecules capable to transform power of sunlight into chemical energy through the dissociation of the water molecule, opens a new era in the study and treatment of eye disorders epidemiologically relevant.

Acknowledgement:

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