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RECURRENT CENTRAL VENOUS RETINAL OCCLUSION, CLINICAL FEATURES AND TREATMENT OUTCOME

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Abstract

Occlusion, thrombosis of the central retinal vein is the second most common vascular disease after diabetic retinopathy. Retinal vein occlusion usually affects the older population.

Hypertension, stroke, advanced age, sex, hyperlipidemia are all significant risk factors. Anti-vascular endothelial growth factor agents have been shown to be effective in improving vision at this condition. Aim of this paper is to describe a 38-year-old woman with a medical history of hypertension who was complaining on blurred vision in the left eye.

After a complete ophthalmological examination, she started with anti-VEGF treatment. After 3 monthly applications of aflibercept according to the T&E protocol, the treatment continued according to the PRN protocol, during which there was an exacerbation of the disease.

Keywords: central retinal vein occlusion, thrombosis, vascular, vascular endothelial growth factor, aflibercept.

Introduction

Occlusion, thrombosis of the central retinal vein, CRVO, is the second most common vascular disease after diabetic retinopathy [1]. Retinal vein occlusion usually affects the older population. There are two types of this acquired retinal vascular disease: ischemic and non-ischemic CRVO [2]. About 20% of CRVO cases are ischemic. The process of transition from non-ischemic to ischemic form of central retinal vein occlusion is very fast and often occurs in the first month after the change occurred [3].

A recent pooled analysis of patients in the United States, Europe, Asia and Australia estimated an overall prevalence of 16.4 million adults with RVO. Of these individuals, 2.5 million have RVO (CRVO) and 13.9 million have branch RVO (BRVO). It is known the incidence increases with age, with more than a half of all cases occurring in patients older than 65 years. The Blue Mountain Study showed a 0.7% incidence in patients younger than 60 years, increasing to 4.6% in patients 80 years and older.

The pathogenesis of CRVO is due to thrombotic occlusion of the central retinal vein (CRV) at, or posterior to lamina cribrosa [4]. Thrombosis increases the retinal capillary pressure, capillary permeability, and leakage of fluid and blood into the retina [5]. In patient with RVO, macular edema (ME) is the most common complication and a major cause of visual impairment.

Excessive production and release of the vascular endothelial growth factor (VEGF) is the main reason for development of ME and retinal hemorrhages [6]. Furthermore, high VEGF levels promote the progression to retinal non-perfusion and ischemia, which in turn can lead to increased VEGF levels, worsening ME and hemorrhages, and resulting in subsequent visual impairment.

Anti-vascular endothelial growth factor (VEGF) agents have been shown to be effective in improving vision and resolving ME [7]. The antiangiogenic treatment involves intravitreal application of a recombinant fusion protein consisting of vascular endothelial growth factor (VEGF)-binding segments from extracellular domains of human VEGF receptors 1 and 2, which are fused to Fc segment of human IgG1 immunoglobulin. In thus inhibits the activity of the vascular endothelial growth factor subtypes VEGF-A and VEGF-B, as well as placental growth factor (PGF), inhibiting the growth of new blood vessels in the choriocapillaris.

Cardiovascular conditions are the most common risk factors for RVO and are more likely to lead to BRVO than CRVO.

Hypertension, stroke, advanced age, sex, hyperlipidemia are all significant risk factors [8]. Hyperlipidemia is a risk factor for both CRVO and BRVO, and occurs more often in young (≤50 years) [2]. The percentage of cases with any form of RVO as a result of hyperlipidemia was 20.1% [3]. Age is very critical factor and has a positive correlation with the disease, where up to 90% of patients in all current case studies are over 50 years. Among other risk factors that attribute to RVO are: retinal microangiopathy, systemic diseases like: oxidative stress, diabetes mellitus (DM), Chronic kidney disease (CKD). Trombotic risk factors such as hyperhomocysteinemia, MTHFR gene mutation, APL, and Lp (a) were also been shown to be independent risk factors of RVO [2]. Hyperhomocysteine (Hhcy), antiphospholipid syndrome (APS), the factor V Leiden, PC, PS antitrombin (AT), glaucoma [2].

Recurrent CRVO refers to multiple episodes of blockage in the central retinal vein, leading to reduced blood outflow from the retina. Symptoms remain consistent with acute RVO episodes: sudden painless decrease in vision, blurry or distorted vision, floaters in the visual field. Recurrence of CRVO in the same eye occurs infrequently and may not be associated with an uncontrolled systemic disease. In younger age patients where there was not found any of the other systemic or trombotic risk factors, hypertension, hyperlipidemia and increased inflammatory cytokines may play the key factor of recurrent CRVO od and recurrent or/and persistent wet macula up to 100 weeks [1]. The LEAVO study and Shuchenko et al. conducted a study monitoring of the morphologic retinal predictors, visual acuity (VA), central sub-foveal thickness (CST) and the drugs response in young and older patients with persistent or recurrence of the disease [14].

Case report

A 38-year-old woman, female, with no family history of autoimmune diseases and a personal medical history of hypertension was admitted to our Ophthalmology Department of the University Eye Hospital 12 months ago complaining on blurred vision in the left eye. On ophthalmic examination, the best corrected visual acuity (BCVA) was 0,9 and central retinal vein occlusion in the left eye was disclosed.

Intraocular pressures were 14 mm Hg in the right, and 17 mmHg in the left eye.

The moment of examination the blood pressure was 140/90 mm/Hg.

Slit lamp exam showed normal anterior segments with open angles bilaterally.

Fundus examination reveled central retinal vein occlusion, superficial flame-shaped retinal hemorrhages, macular and optic nerve papilledema.

The right eye examination showed grade 1 (Barely detectable arterial narrowing).

Posterior findings on optical coherence posterior segment tomography (PS-OCT) were: hemorrhages in all 4 retinal quadrants on the left eye fundus photography, macular edema with central sub-foveal thickness of CST=367 µm on OCT. On average retinal nerve fiber layers the TT was 261 µm, and Cup Volume of 0.00 mm^3 presenting edema of the optic nerve (Figure 1).

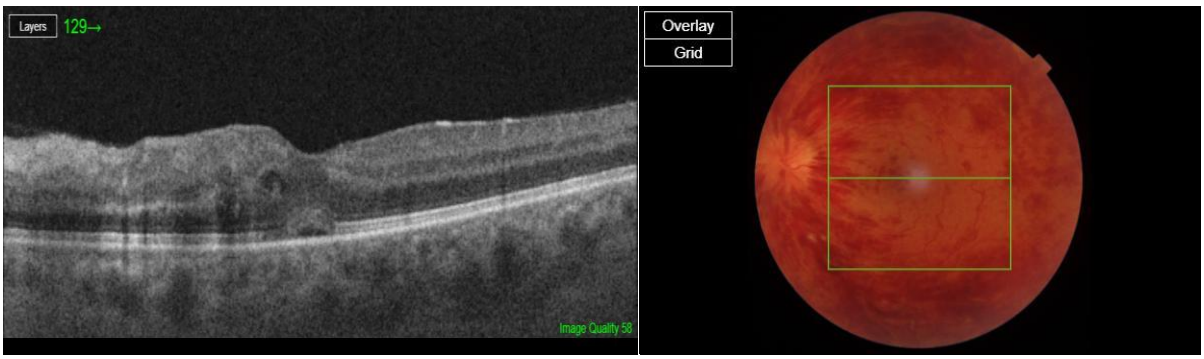

Figure 1. Optical coherence posterior segment tomograph

Table 1. Laboratory test including hypercoagulability workup

Sed	8	10/20
WBC	8.2	3.5-10
RBC	4.7	3.8-5.8
HGB	144	110-165
HCT	0.433	0.35-0.5
MCV	92.1	80-97
MCH	30.6	26.5-33.5
MCHC	333	315-350
PLT	221	150-390
RDW-SD	39.8	37-54
RWD-CV	12.2	11-16
PDW	9.8	10-18
MPV	8.8	6.5-12
P-LCR	16.6	13-43
PCT	0.19	0.1-0.5
NEUT	5.15	1.2-6.8
LYMPH	2.23	1.2-3.2
MONO	0.71	0.3-0.8
EO	0.08	<0.4
BASO	0.03	<0.1
NEUT %	62.7	43-76
LYMPH %	27.2	17-48
MONO %	8.7	4-12
EO %	1	<6
BASO %	0.4	<1
GLY (mmol/L)	6.82	3.5-6.2
Urea	4.4	3.2-8.3
D-Dimer	0.161	<0.5
Urinary Status		
Ph	5.5	4.6-6.4
WBC	Neg	neg
RBC	50	neg
Nitrates	Neg	neg
Prot	Neg	neg
Ascorbit acid	Neg	
GLY	Norm	neg
Ketons	neg	neg
Urobilinogen	norm	neg
Bilirubin	neg	neg
sed-rbc	0-5	<5
sed-wbc	0-5	
sed-kristal	neg	

We started the treatment with an anti-VEGF drug aflibercept which according to our previous experience and world study cases is not inferior to bevacizumab or ranibizumab.

At base line one dose was administrated. Three weeks later on the first control BCVA was 1,0. The patient received additional 2 monthly doses (total of 3 doses of aflibercept). Four weeks later on second control, on OCT there is a rest of small cysts filled with small amount of fluid in the papillary-macular area. Central subfield thickness was reduced of CST= 228μm. (Figure 2)

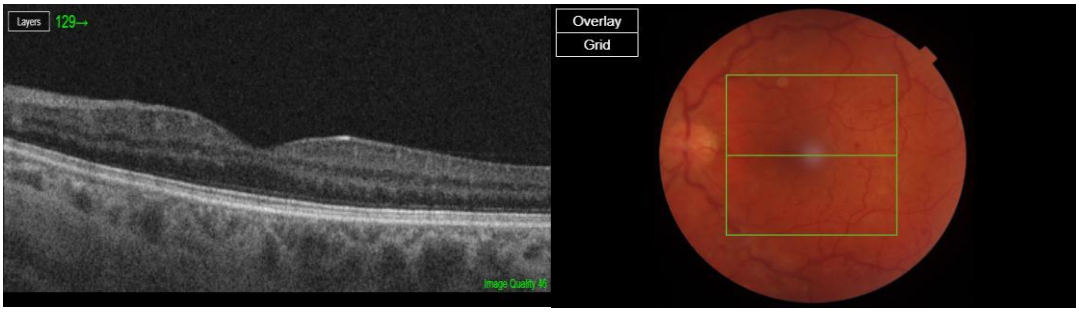

Figure 2. Control optical coherence tomography after 3 monthly applications of aflibercept

On fundus photo: markedly dilated venous blood vessels, cotton wool exudates along the length of the venous arches, hemorrhages in stage of resorption. The presence of collateral blood vessels in the medial-retina and at the level of papillary optic nerve (PNO) was found.
A month later she shows up at our clinic with blurred vision on the same eye.
Her BCVA is: 0.7 and now she has a recurrent CRVO.
On OCT findings we have: intra-retinal fluid (IRF) with centrally confluent large bullous spaces followed by changes at the integrity of the plexiform layer, intra-retinal hemorrhages with notable thickening of the macula CST=504 µm. (Figure 3).

We performed optical coherence tomographic angiography (OCTA) (Figure 4), and fluorescein fundus angiography imaging (FFA), (Figure 5).

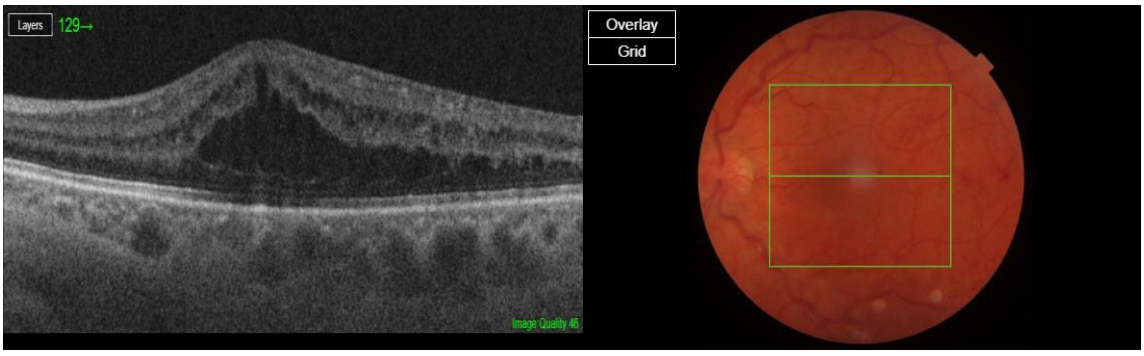

Figure 3. Exacerbation of the finding shown on optical coherence tomography

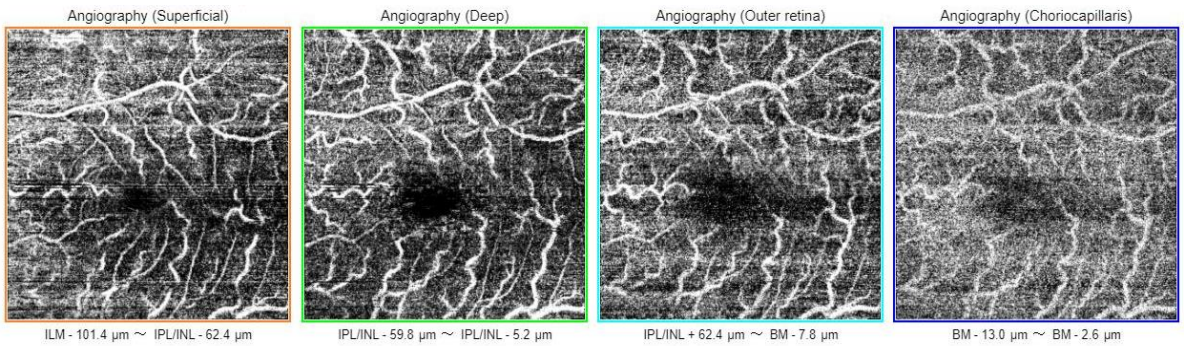

Figure 4. OCTA finding of: dilated and tortuous veins, narrowed arteries, ischemic zones in the inner and outer layers.

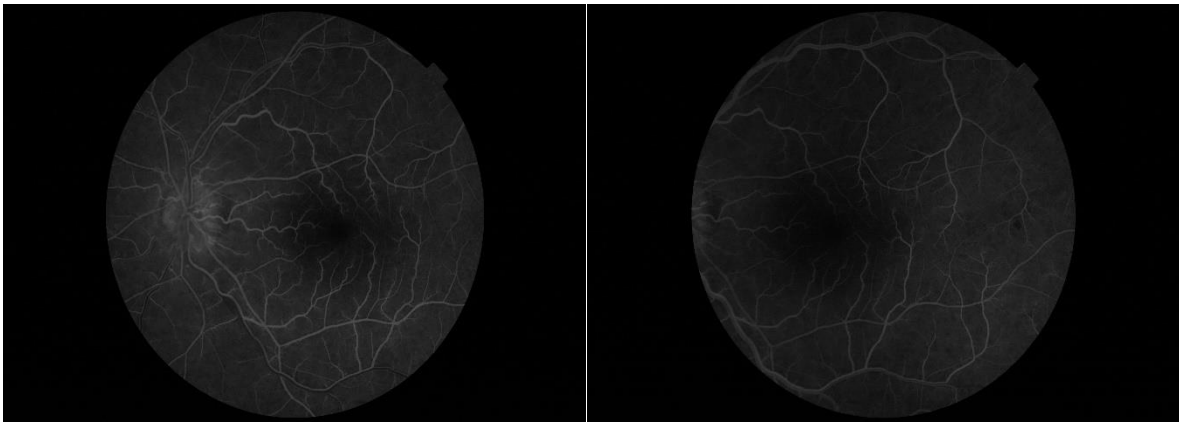

Figure 5. Fluorescein fundus angiography imaging

Again we started treating the patient with anti-VEGF agents. She received four loading monthly doses of aflibercept. Her condition got better, as well as the BCVA. She gain 3 lines, and BCVA of 0,9. The central macular thickness decreased of CST= 430μm, (Figure 6).

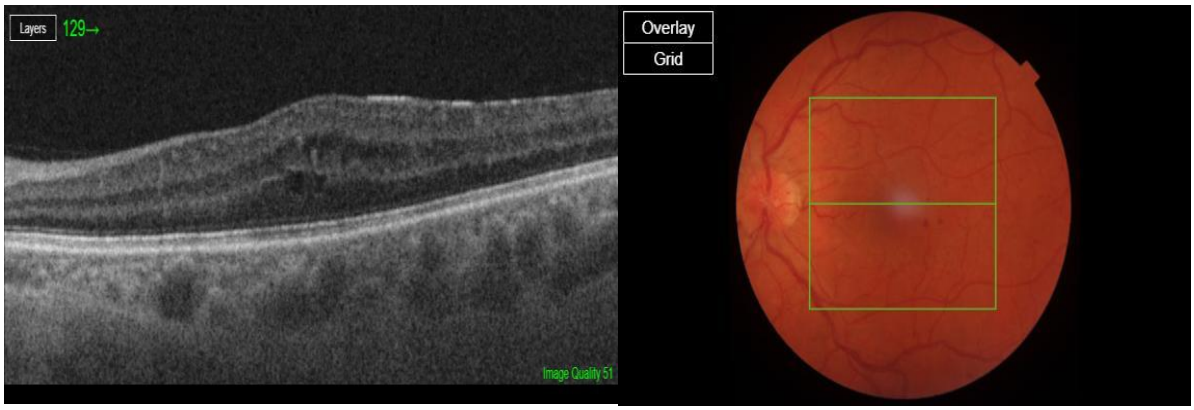

Figure 6. OCT: intra-retinal foveal cysts (IRCs), still wet macula, small foveolar disruption on the photoreceptor layers.

Because of the persistence of residual fluid we decided to administrate another dose of the drug, make control imaging and continue with 4 to 8 monitoring visits and treat and extend
(T&E) regimen in the first year of treatment.

Discussion

Central retinal vein occlusion is a disease of the old population. Paul O'Mahoney et al. studied the relationship between traditional atherosclerotic risk factors and retinal vein occlusion (RVO). They systematically retrieved all studies between 1985 and 2007 that compared cases with any RVO with controls. They concluded that hypertension and hyperlipidemia are common risk factors for RVO in adults, and diabetes mellitus is less so. It remains to be determined whether lowering blood pressure and/or serum lipid levels can improve visual acuity or complications of RVO [1].

In view of the evidence that drug treatment of hypertension may reduce same hypertensive complications, particularly cerebrovascular episodes, it seems likely that good control of hypertension should reduce the mortality of retinal vein occlusion from vascular causes and possibly recurrence of retinal vein occlusion.

The exact mechanism of retinal venous damage by hypertension is unclear but possibilities include increased inflammatory activity, which has been demonstrated in hypertensive patients with retinal vein occlusion, or indirect vascular damage to the retinal vein [2]. This in turn may lead to vascular degeneration, with deposition of platelet aggregates. Nowadays the choice of treatment in CRVO with consecutive ME is administration of anti-VEGF medicaments. People with CRVO and ME manifest marked heterogeneity in treatment response. According to Early Treatment Diabetic retinopathy Study (ETDRS) younger age, higher baseline BCVA, and a definitely intact baseline sub-foveal ellipsoid zone were independent predictors of final BCVA [3].

Baseline CST on spectral-domain optical coherence tomography (OCT) was not found to be a predictor for final BCVA score.

In our case we have a young female patient with poor control of blood pressure. She had a recurrent CRVO on the same eye. Based on the LEAVO study intraocular VEGF levels could be sufficiently suppressed by anti-VEFG therapy. In contrast, although the VEGF drive in eyes with recurrent ME is intermittently suppressible, these eyes may have entered a self-perpetuating cycle of VEGF-induced retinal vascular permeability, probably from retinal ischemia.

Lower VEGF concentrations are required to trigger recurrent ME compared with that required for developing iCRVO. Also in young patients concentrations of cytokines probably plays more prominent role in recurrence and wet macula. Higher systolic blood pressure was associated with wet macula as well. Previous studies have shown that larger fluctuations of retinal fluids can lead to poorer VA outcomes because of the impact on retinal cells, potential mechanical stress to retinal photoreceptor layers and decreased visual function [4]. So according to all of this in cases like ours if an eye can achieve CST less than 320μm after the loading baseline treatment and the same eye develops recurrent ME, and if that macular edema does not result in intermittent high CST VA gains can be sustained [2].

This can be better achieved with the treat-and-extend (T&E) regime of treatment rather than pro re nata regimen. However, this hypothesis must be proven by many future studies.

Conclusion

Central venous occlusion is not such a rare condition in young patients. Risk factors for this condition should be found and treated if necessary. Treatment with an anti-VEGF agens (aflibercept) with a T&E protocol has been shown to be superior to PRN in our case.

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