The Importance of Specific Antibiotic Therapy in the Evolution of Retinal Vasculitis

NICOLETA ANTON[1]*, ANISIA IULIANA ALEXA[1], ALINA CANTEMIR[1], BOGDAN MIHNEA CIUNTU[2]*, DANIEL TIMOFTE[2], CAMELIA MARGARETA BOGDANICI[1], ROXANA ELENA CIUNTU[1]

[1] Grigore T. Popa University of Medicine and Pharmacy Iasi, Faculty of Medicine, Ophthalmology Department, 16 Universitatii Str.,700115, Iasi, Romania

[2] Grigore T. Popa University of Medicine and Pharmacy Iasi, Faculty of General Medicine, Surgery Department, 16 Universitatii Str., 700115, Iasi, Romania

Ischemic retinal vasculitis is an inflammation of retinal blood vessels associated with vascular occlusion and retinal hypoperfusion. It may cause visual loss secondary to macular ischaemia, macular edema and neovascularization leading to vitreous hemorrhage, fibroblastic proliferation and retinal detachment by traction. Corticosteroids with or without immunosuppressive medication are the main treatment in retinal vasculitis associated with laser photocoagulation of retinal ischemic regions. In Lyme's disease, etiologic treatment is achieved with Ceftriaxone that can be associated in some cases with corticosteroids. In this paper, we report about a patient who presented for the decrease of about 1.5 months of painless, asymptomatic visual acuity (VA). The patient was diagnosed with oclusive retinal vasculitis and followed a series of investigations to identify the etiology. The presence of anti-borelial antibodies required the administration of specific treatment with ceftriaxone 1g / 12h to which was added after 48h systemic corticosteroids, with slow evolution favourable. This association of retinal vasculitis - Lyme was quite rare and difficult to demonstrate. The prognosis of patients with retinal vasculitis is variable. Many patients may have a relatively benign condition or may have a dramatic response to systemic imunosuppressive therapy and will retain visual function. In the long run, despite specific treatment, it is unfavorable due to the evolution of retinal atrophy with visual field and visual function. Patients with ischemic retinal vasculitis represent a significant management challenge and, if not treated properly, can lead to a severe, irreversible visual loss.

Keywords: ceftriaxone, inflamatory , Lyme disease, retinal vasculitis

Retinal vasculitis is an inflammation of retinal blood vessels associated with vascular occlusion and subsequent retinal hypoperfusion. It may cause visual loss secondary to macular ischaemia, macular edema and neovascularization leading to vitreous hemorrhage, fibrovascular proliferation and retinal detachment by traction. Retinal ischemic vasculitis may be idiopathic or secondary to systemic disease, such as Behcet disease, sarcoidosis, tuberculosis, multiple sclerosis and systemic lupus erythematosus [1-3].

The pathogenesis of ischemia in retinal vasculitis is unclear, but it is suggested to be either thrombotic or obliterant secondary to infiltration of inflammatory cells. Based on histological studies, vascular changes in uveitis are characterized by perivascular infiltration of lymphocytes that result in perivasculitis rather than true vasculitis of the vessel wall. Thrombotic vascular changes may occur due to local endothelial lesion or increased prothrombin activity as observed in Behcet's disease [3]. Vascular changes involving veins are more likely to be associated with Behcet's disease, sarcoidosis, tuberculosis, multiple sclerosis, HIV infection, Eales disease, and those involving arteries have systemic lupus erythematosus and nodular polyarteritis.

Experimental part

We present the case of a 45-year-old male patient in the urban environment, professional driver who was admitted in the I Ophthalmology clinic accusing the decrease in visual acuity at both eyes (AO), without simptoms about 1.5 months. From the personal pathological history: The patient does not declare. The specialty examination finds the following: visual acuity VARE=0.2 fcnc si VALE=0.1fcnc. Slit lamp examination at both eyes: only conjunctival hyperaemia. *The AO eye exam reveals : RE (right eye)* Optic nerve have net contour, normal dye, dilated and incised veins in the inferior artery along the arches, numerous spot and spot bleeds, dull exudates, neurosensory retinal detachment in the interpapillomacular space and moderate subretinian fluid in the macular area and *LE* (left eye) optic nerve well- defined, numerous telangiectasia on the surface of the haemorrhage in the point and the stain along the upper temporal arches, the dilated veins, the retrieval of the neurosensory retina in the interpapillomacular space)(fig. 1).

The OCT (ocular computer tomography) exam show the presence of an important neurosensory retina decolation with a significant amount of subretinal fluid (fig. 2) The review of systems was unremarkable. Laboratory

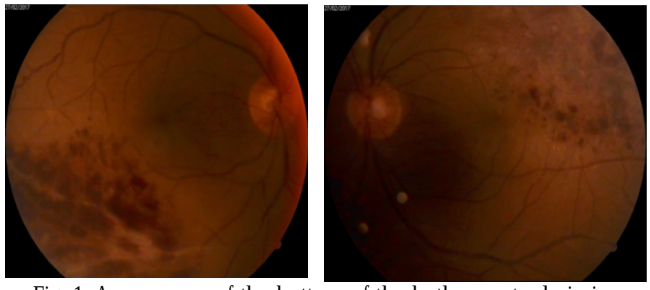

Fig. 1. Appearance of the bottom of the both eye at admission

* email: dr.nicoletaanton@yahoo.com; bogdanmciuntu@yahoo.com

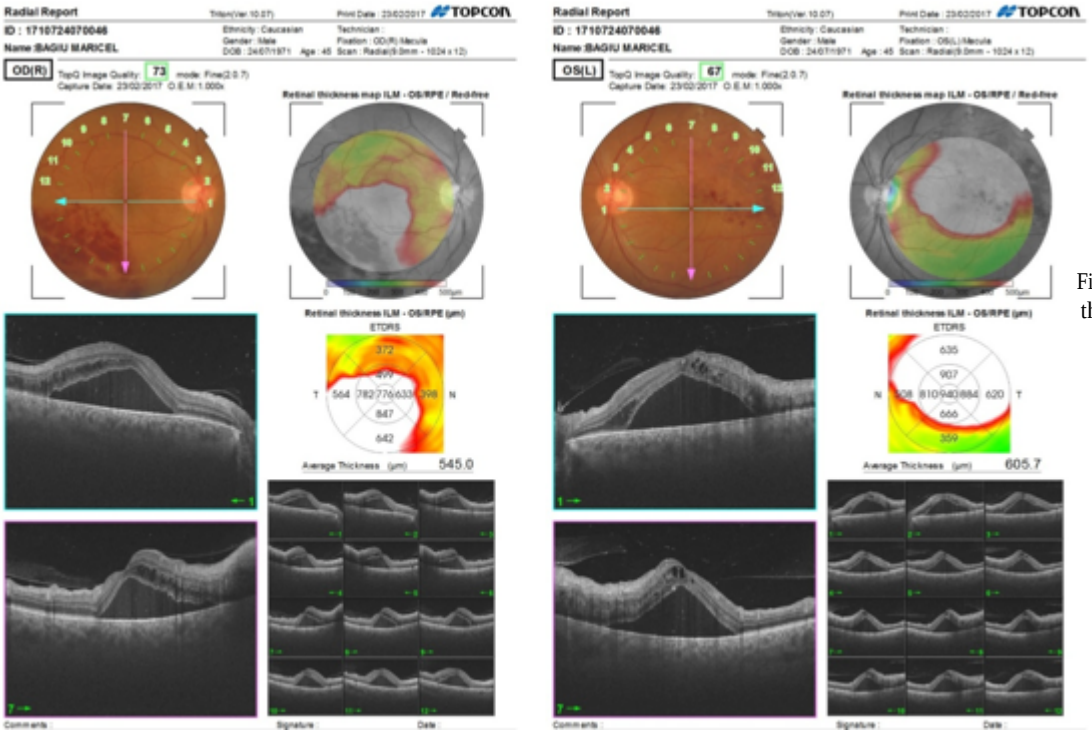

Fig. 2. Appearance OCT of the both eye at admission

workup was negative, including complete blood count, sedimentation rate, creatine protein, angiotensin converting enzyme level, antinuclear antibodies, quantiferon gold, and fluorescent treponemal antibody absorption assays (fig. 3). Only test for Borrelia burgdorferi was positive, increased anti-borrelia-IgM titres> 0.53mg / dl (normal values are considered below 0.20) with normal IgG levels. The patient was diagnosed with ocular retinal vasculitis, serous neurosensory retinal detachment, and Lymes Disease. Treatment with Ceftriaxone 1g / day was initiated for 21 days, and at 48 h, Medrol was initially added at 64 mg / day, then decreasing with 2 months, topical Netildex inhaled both eyes 4 times / day, with a slow progression.

At the one-month control, there is a slow increase in VA at RE and the same at LE, LE discal neovascularization, reduction of haemorrhages and subretinal fluid at both eyes (retinal center thickness is reduced to RE-426 vs 606µm, LE 482 Vs 854µm). Therapeutic conduct consisted of continued anti-inflammatory treatment, an intravitreal injection of anti-VEGF in the OS. Due to the unfavorable evolution at 2 months when there are new changes in FO (fundus appearance of capillary dilatations on the dox and whitish deposits on the posterior hyaloid, the arteries and veins are narrowed into whitish cords) (fig. 3), persistence of the subretinal fluid in a moderate amount, The subtonic injection of Triamcinolone acetonide to AO is determined and programming for AO laser photocoagulation. At 3 months, a stationary appearance at OD was found but with a slight decrease of AVOS, with PIO increase to

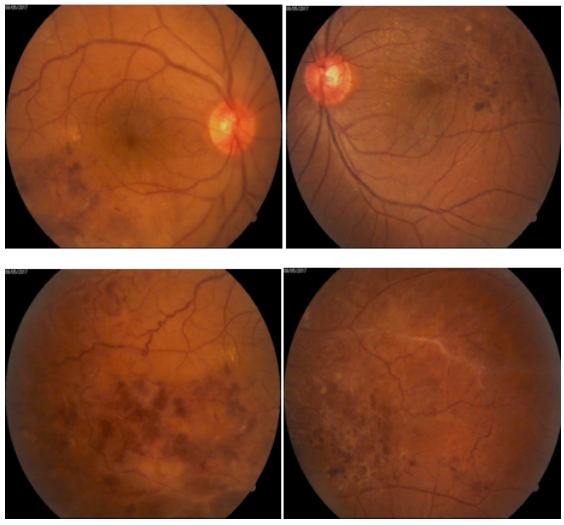

Fig. 3. Appearance of the bottom of the both eye at 2 months

40mmHg requiring the addition of topical antiglaucoma medication (Cosopt and Brimonal) and continued AO laser photocoagulation. At the last visit, at 6 months, the general and ophthalmological status is stationary, with the improvement of VA to AO (VARE = 0.5fcnc, VALE = 0.4fcnc), maintenance of an IOP increased (38mmHg) and persistence of a reduced amount of subretinal fluid macular. The OCT reveals a significant reduction in central retinal thickness and subretinal fluid compared to the first visit (table 1). Specific anti-inflammatory and anti-inflammatory treatment has led to a favorable prognosis

Retinal central thickness	RE (right eye)	LE (left eye)
At admission	606µm	854µm
At 3 months	442µm	719µm
Last visit	435 µm	361 µm

Table 1
EVOLUTION OF RETINAL CENTRAL THICKNESS ON OCT

in the short term but with an uncertain, long-term prognosis due to sequelae appear after reduction of edema, haemorrhage and secondary laser photocoagulation (affecting visual field and visual function).

Results and discussion

Retinal ischemic vasculitis is an inflammation of retinal blood vessels associated with vascular occlusion and retinal hypoperfusion. Ischemic retinal vasculitis may be idiopathic or secondary to systemic disease, such as Behcet's disease, sarcoidosis, tuberculosis, multiple sclerosis and systemic lupus erythematosus. The main concern in retinal vasculitis is vascular occlusion and secondary retinal ischemia which can lead to severe impairment. The pathogenesis of ischemia in retinal vasculitis is unclear, but it is suggested to be either thrombotic or obliterant secondary to the infiltration of inflammatory cells. Based on histological studies, vascular changes in uveitis are characterized by perivascular infiltration of lymphocytes resulting in perivasculitis rather than true vasculitis of the vessel wall [3,4]. Cell mediated immunity also plays a role in the retinal vascular pathology, with CD4 + T cells documented inside and around the retinal vessels. Retinal vascular obstruction may also promote the production of vascular endothelial growth factor (VEGF), which increases vascular permeability and results in macular edema and induced neovascularization [5]. Angiogenesis is initiated by the cell bed microdeformation that cause local hypoxia and thus leads to an increase in the vascular endothelial growth factor (vascular endothelial growth factor - VEGF). The temporary reduction of blood flow to the edges of the wound stimulates angiogenesis through hypoxia-inducible factor (HIF) -1alfa -> VEGF with an increase in density of microcirculation [6].

Oxygen free radicals (superoxide anion, hydroxyl radical etc) produced in excess stimulate lipid peroxidation of the polyunsaturated fatty acids forming, thus, in excess, lipid-peroxil radicals. These radicals stimulate in their turn the oxidation of the low-density lipoproteins (LDL), favouring angiopathy [7]. The superoxide radical is involved in various physiological and pathophysiological processes. It is produced in respiratory and cytochome P450 electron transport chain reactions as a by-product. A high amount of this product is also generated by activated neutrophils and macrophages during oxidative burst [8].

The physiopathology of the changes in the lipid metabolism of diabetes mellitus is multifactorial and incompletely deciphered. Quantitative anomalies of lipoproteins (LP) consist of increasing levels of triglycerides as the very low-density lipoprotein (VLDL) and IDL and decreased levels of high-density lipoprotein cholesterol (HDLc) due to the decrease of the subfraction HDL2. The decrease of HDLc is due to the rise in its catabolization [9].

The macrophages, T cells and cytokines (Interleukin-1-beta) cooperate in synergy to destroy B cells [10]. The possibility of identifying and differentiating infectious and non-infectious causes is very important in adopting the therapeutic course that varies depending on the cause. In cases with a large number of days of hospitalization during which surgery was performed that targeted the digestive tract there are studies which confirm the appearance of endogenous fungal endophthalmitis after recent surgery (11).

Lyme disease is a multisystemic disease caused by the spore Borelia Burgdorferi, which is transmitted through the bite of infected ticks. Eye manifestations may involve any of the eye structures and may occur at any stage. Retinal vasculitis is commonly associated with intraocular inflammation. In the differential diagnosis of retinal vasculitis, Lyme disease should also be considered in endemic areas for the disease. Diagnosis is based on the clinical aspect. Diagnosis is based on ocular and systemic clinical findings, antibiotic antibiotic burgdorferi determination in immunoglobulin blood (Western blot) or ELISA (Enzyme-linked immunosorbent assay), excluding other infections and inflammatory causes [4, 5,12] . Once diagnosed, the specific therapy in borreliosis is based on the degree of early or late impairment and neurological involvement. The recommended treatment for early localized impairment is oral doxycycline 200mg / day 21-28 days, and intravenous therapy with Ceftriaxone 2g / day 21-28 days is important in neurological impairment. Some studies have shown similar efficacy of the two without regard to the route of administration [13,14]. In our case, the use of antibiotic therapy alone was not sufficient, the presence of neurosensory retinal detachment required the addition of a general anti-inflammatory and / or subtenonic injection, to reduce ocular inflammation and to prevent the occurrence of complications with slowly favorable evolution. Studies show that simultaneous anti-inflammatory anti-inflammatory therapy is possible, especially in severe, bilateral inflammations. Also, intraocular injection of anti-inflammatory is recommended in refractory cases of macular edema. Absence of corticosteroid response requires the use of immuno-suppressants (azathipine, ciclosporin, cyclophosphamide, etc.). Other treatment modalities in systemic vasculitis are retinal laser photocoagulation and vitrectomy in complicated cases with retinal neovascularization or vitreous haemorrhage [2,13,14]. Studies suggest that corticosteroids with or without immunosuppressive medication are the main treatment in retinal vasculitis associated with laser photocoagulation of retinal ischemic regions. Intravitreal injections of bevacizumab are used to treat secondary neo-vascularization, but should be performed concurrently with laser retinal photocoagulation to prevent subsequent retinal ischemia [2,14].

The prognosis for patients with retinal vasculitis is variable. Many patients may have a relatively benign condition or may have a dramatic response to systemic immunosuppressive therapy and will retain visual function. Other patients are more resistant to therapy and, despite the use of aggressive treatment, will experience permanent visual impairment. Permanent patient monitoring is very important [15].

Conclusions

Retinal vasculitis is an intraocular inflammation that threatens vision, affecting retinal vessels. It may appear as an isolated ocular state as a manifestation of infectious or neoplastic disorders or in association with a systemic inflammatory disease. The search for a fundamental etiology should be addressed in a multidisciplinary way based on a thorough history, system review, physical examination, and assessment of laboratory exams. Patients with ischemic retinal vasculitis represent a significant management challenge and, if not treated properly, can lead to a severe, irreversible visual loss. Patients with ocular damage to Lyme disease should be fully investigated to rule out other possible aetiologies. The literature suggests that it is difficult to demonstrate that retinal changes are due exclusively to Lyme disease. The specific therapy with Ceftriaxone associated with systemic anti-inflammatory has been a useful therapeutics in our case of severe, bilateral retinal vasculitis associated with

Lyme Disease. Longitudinal or prospective studies are required to evaluate the efficacy of therapies in preventing the progression of occlusive retinal vasculitis and its complications.

References

1.ROSENBAUM, T., KU, J.,. ALI, A., CHOI, D., SUHLER, E.B.,Patients with retinal vasculitis rarely suffer from systemic vasculitis, Seminars in Arthritis and Rheumatism, vol. 41, no. 6, pp. 859–865, 2012.

2.SHRESTHA J K, KHADKA D, LAMICHHANE G, KHANAL S. Retinal vasculitis. Review article. Nep J Oph 2009;1(1):66-71

3.LAZHA TALAT, SUE LIGHTMAN, OREN TOMKINS-NETZER,. Ischemic Retinal Vasculitis and Its Management.Review article .Hindawi Publishing Corporation. Journal of Ophthalmology. Volume 2014, Article ID 197675, 13 pages. http://dx.doi.org/10.1155/2014/197675;

4.AHMED M. ABU EL-ASRAR, CARL P. HERBORT, KHALID F. Tabbara. Retinal Vasculitis. Review. Ocular Immunology and Inflammation, 13:415–433, 2005. DOI: 10.1080/09273940591003828

5.***American Academy of Ophthalmology- Intraocular inflammations and uveites, Basic and Clinical Science Cource, 2016-2017;

6.CIUNTU, B.M.; VASILUTA, C.; NEGRU, R.; HULTOANA, R.; CIUNTU, R; GEORGESCU, ST.O; SARBU, P.D.;AZOICAI, D. Negative Pressure Therapy in the Surgical Treatment of Diabetic Foot, Rev. Chim. (Bucharest), **68**, no. 7, 2017, p. 1648

7.BADESCU, L; BADULESCU, O; BADESCU, M; CIOCOIU, M. Natural polyphenols improve the dislipidemy and eye complications in the experimental diabetes mellitus, Romanian Biotechnological Letters, 2012, 17(4): 7397-7407;

8.BADESCU, L; BADULESCU, O; BADESCU, M; CIOCOIU, M. Mechanism by Sambucus nigra Extract Improves Bone Mineral Density in Experimental Diabetes, EVIDENCE-BASED COMPLEMENTARY AND ALTERNATIVE MEDICINE, 2012,Article Number 848269;

9.BADULESCU, O; BADESCU, C; CIOCOIU, M; BADESCU, M. Interleukin-1-Beta and Dyslipidemic Syndrome as Major Risk Factors for Thrombotic Complications in Type 2 Diabetes Mellitus, Mediators of Inflamation, 2013 (2013), Article Number 169420;

10.BADESCU, L; BADULESCU, O; CIOCOIU, M; BADESCU, M. Modulation of neuropathic pain in experimental diabetes mellitus, Journal of Physiology and Biochemistry, 2014, 70(2): 355-361;

11.ANISIA, E.I; CIUNTU, R ; CANTEMIR,A; ANTON, N; DANIELESCU, C; NEGRU, R.; BOGDANICI,C.M.; VASILUTA, C.; GEORGESCU, ST.O; SARBU, P.D.;CIUNTU, B.M. The Importance of Fluconazole in Treament of Endogenous Endophthalmitis in Patients Prior Treated Using Negative Pressure Therapy for Wound Closure Contaminated with Methicillin-resistant Staphylococcus aureus, Rev. Chim.(Bucharest), **68**, no.7, 2017, p.1598-1601;

12.CERVERA, R.,Update on the diagnosis, treatment, and prognosis of the catastrophic antiphospholipid syndrome, Current Rheumatology Reports, vol. 12, no. 1, pp. 70–76, 2010

13.***FDA Public Health Advisory: Assays for Antibodies to Borrelia burgdorferi: Limitations, Use, and Interpretation for Supporting a Clinical Diagnosis of Lyme Disease. U.S. Government Printing Office: 1997 - 520-050. July 7, 1997.

14.BREMELL,D., DOTEVALL,L., Oral Doxycycline for Lyme Neuroborreliosis with simptoms of encephalitis, myelitis, vasculitis or intracranial hipertension. European Journal of Neurology 2014.21: 1162-1167. Doi: 10.11111/ene.12420

15.MORA,P., CARTA, A., Ocular manifestations of Lyme borreliosis in Europe. Int. J. Med. Sci. 2009, 6(3):124-125

Manuscript received: 14.03.2017