Polskie Towarzystwo Okulistyczne
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KLINIKA OCZNA 2023, 125, 1: 50-55
Received: 20.11.2021 Accepted: 28.04.2022

CASE REPORT

Access this article online

Website:
www.klinikaoczna.pl

DOI:
https://doi.org/10.5114/ko.2022.118406

Idiopathic retinal vasculitis, aneurysms and neuroretinitis (IRVAN): a case report and outcomes of 1.5-year observation

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ABSTRACT

Introduction: Idiopathic retinal vasculitis, aneurysms and neuroretinitis (IRVAN) syndrome is a rare clinical entity of unknown etiology with vision threatening potentials.

Case presentation: In this article, we present a case of a 38-year-old woman complaining of decreased visual acuity OU (oculi utriusque) for a duration of 3 months. On admission, the best-corrected visual acuity (BCVA) was 5/50 in the right eye (RE) and 2/50 in the left eye (LE). Mild rubeosis iridis in the LE was noted. Posterior segment examination revealed hemorrhage floaters in the vitreous chamber, macular edema, hemorrhages and aneurysms in OU. Fundus fluorescein angiography (FFA) showed the presence of numerous microaneurysms, enhancement of vascular contrast, leakage on the optic nerve disc, as well as extensive areas of non-perfusion in the middle peripheral retina in OU. Based on constellation of clinical and angiographic features as well as the negative extensive workup, a diagnosis of IRVAN was established. Anti-inflammatory, immunosuppressive and hemostatic treatments were applied, and panretinal photocoagulation was performed in OU. In the next stage, due to visual impairment, persistent vascular leak, macular edema in OU, anti-vascular endothelial growth factor (VEGF) intravitreal injections were given. As a result, BCVA increased to 5/12 in the RE and 5/50 in the LE. The patient remains under regular follow-up.

Conclusions: Late diagnosis and lack of appropriate treatment of IRVAN syndrome may lead to complete loss of vision due to complications secondary to lack of perfusion. It is important for ophthalmologists to improve understanding of this disease and manage the symptoms as soon as possible.

KEY WORDS: IRVAN syndrome, retinal vasculitis, aneurysmal dilatation, neuroretinitis, panretinal photocoagulation.

INTRODUCTION

Idiopathic retinitis, vasculitis, aneurysms and neuroretinitis (IRVAN) syndrome is a rare, mostly bilateral, retinal vasculitis of unknown etiology. The disease affects mainly healthy individuals with an average age at presentation of 30-40 years and has a female predominance. Idiopathic retinitis, vasculitis, aneurysms and neuroretinitis is a diagnosis of exclusion with no specific tests [1-3]. The constellation of clinical features for the diagnosis is based on three major criteria, including multiple aneurysmal dilatations at arterial bifurcations, retinal vasculitis and neuroretinitis, as well as three minor fundus findings such as peripheral capillary non-perfusion, retinal neovascularization and macular edema [1].

The staging of IRVAN syndrome based on ocular findings was defined by Samuel *et al.* [2] (Table I). Moreover, Qi *et al.* [4] propose adding vitreoretinal fibrovascular proliferation and retinal detachment to the stage 4. In the early stages inflammation predominates, whereas in the later stages prevail complications from ischemia. The natural course of IRVAN syndrome can be devastating and lead to loss of vision due to persistent progression of non-perfusion of peripheral blood capillaries, retinal and optic nerve head neovascularization, neovascular glaucoma as well as development of vitreoretinal fibrovascular proliferation, tractional retinal detachment and exudative maculopathy [1-4]. The management of IRVAN syndrome is based on the clinical stage and complications of the disorder [2] (Table I).

CASE REPORT

A 38-year-old Caucasian woman presented to our clinic complaining of painless deterioration of vision in OU (oculi utriusque) for the three months. There was no previous

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Table I. IRVAN syndrome staging system and suggested treatment

Stage	Ocular findings	Suggested treatment
1	Macroaneurysms, exudation, neuroretinitis, retinal vasculitis	High-dose prednisone, steroid-sparing drugs (e.g., mycophenolate mofetil), photocoagulation, local steroid injections
2	Capillary nonperfusion (angiographic evidence)	
3	Posterior segment neovascularization of disc or elsewhere and/or vitreous hemorrhage	High-dose prednisone, steroid-sparing drugs (e.g., mycophenolate mofetil), photocoagulation, local steroid injections, anti-vascular endothelial growth factor (VEGF) agents, cryotherapy
4	Anterior segment neovascularization (rubeosis iridis)	Surgery, anti-VEGF agents, cryotherapy
5	Neovascular glaucoma	Surgery and treatment for glaucoma

history of eye diseases, surgery or trauma. Her medical history included hypothyroidism. In the initial examination, the best-corrected visual acuity (BCVA) was 5/50 in the right eye (RE) and 2/50 in the left eye (LE). Intraocular pressure (IOP) was 16 mmHg OU. There was no anterior chamber or vitreous inflammation, but mild iris rubeosis in the LE was observed. Fundus examination revealed hemorrhagic floaters in the vitreous chamber. Bilaterally in the eye fundus, there were: macular edema, retinal hemorrhages and arterial aneurysms (Figure 1 A, B).

During fundus fluorescein angiography (FFA), visualization was difficult due to haze from vitreous hemorrhage. The examination showed hyperfluorescence in the projection of numerous saccular microaneurysms within the macula and in the middle peripheral area. Irregular areas of hypofluorescence were present in the macula. Extensive areas of non-perfusion were visualized, beginning in the proximal peripheral area, temporally from the macula, and in the remaining quadrants, in the middle peripheral area. On the border with the non-perfusion zones there were tortuous and saccular-dilated vessels, anastomoses and enhancement of vascular contrast. In the RE, there was a leakage on the optic disc in the late phases. In the LE, there were also superiorly punctuate areas of fluorescence blockage in the projection of hemorrhages (Figure 2 A-D).

Laboratory results were within reference ranges, including complete blood count, sedimentation rate, C-reactive protein, random blood sugar level, urine test, renal function tests, activated partial thromboplastin time (aPTT), international normalized ratio (INR), liver enzyme, homocysteine, and angiotensin converting enzyme (ACE). Results of B-hCG pregnancy testing were negative. Infectious workup revealed positive IgG antibodies against Cytomegalovirus and *Toxoplasma gondi*i as well as positive IgM (0.91) and IgG (1.13) antibodies against Herpes virus (the normal range: < 0.8 ratio). *Bartonella henselae*, *Borrelia burgdorferi*, QuantiFERON-TB Gold, Venereal Diseases Research Laboratory (VDRL) and HIV test were negative.

Rheumatoid factor (RF), anti-double stranded-DNA (anti-dsDNA) antibodies, perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies (pANCA, cANCA), lupus anticoagulant (LAC), and anticardiolipin antibodies (aCL) were within normal limits. The only positive test was antinuclear antibody (ANA) with serum titer of 1:1000 (the normal range: < 100), however, extending the diagnostic panel showed that the presence of anti-Dense Fine Speckled 70 (DFS70) antibodies was responsible for this result. There was no history of fever, oral or genital ulcers, pulmonary or cutaneous manifestation, joint inflammation. Physical examinations did not show any abnormalities. The results of chest radiograph and abdominal ultrasonography (USG) were unremarkable.

Based on constellation of clinical and angiographic features as well as elimination of potential underlying systemic conditions, a diagnosis of IRVAN syndrome was established (the RE was diagnosed as stage 3 and LE as stage 4). Bilateral panretinal photocoagulation (PRP) was performed to prevent neovascular complications of extensive peripheral non-perfusion. During hospitalization the patient received 1 g of methylprednisolone intravenously once daily for 3 days, 500 mg etamsylate per os twice daily and 800 mg acyclovir per os five times daily. Improvement was achieved after the applied treatment and at discharge BCVA reached 5/25 in the RE and 5/50 in the LE. Further treatment consisted of 20 mg of methylprednisolone per os (with tapering the dose) as well as etamsylate and acyclovir. Troxerutin and bromfenac was administered twice daily to OU. During a follow-up due to persistent neovasularization of the optic disc in the RE, complementary argon laser photocoagulation to ischemic regions was performed.

At the 2-month follow up, the patient complained of black shadow in the RE which was vitreous hemorrhage resulted most likely from retinal or optic disc neovascularization. Best-corrected visual acuity decreased to 2/50 in the RE and 1/50 in the LE. Patient received 2 intravitreal injections of aflibercept to OU to treat macular edema (Figure 3 A, B). Moreover, the treatment was modified to 500 mg mycophenolate mofetil per os once daily and 16 mg of methylprednisolone per os (with tapering the dose). After 10 months BCVA increased to 5/12 in the RE and 5/50 in the LE. There was reduced macular thickness, but also increased deposition of exudates, atrophy of retinal neuroepithelium and epiretinal membrane (ERM) on OCT (Figure 3 C, D).

Six months later, repeated FFA of OU disclosed the presence of massive leakage suggesting persistent retinal vasculitis. OCT showed increased exudates and cystoid macular edema bilaterally. Best-corrected visual acuity was 5/16 in the RE and 5/50 in the LE. The follow-up evaluation of blood count and the coagulation system was normal. Diagnostics was extended to chest computed tomography (CT), brain magnetic resonance imaging (MRI) and carotid arteries Doppler ultra-

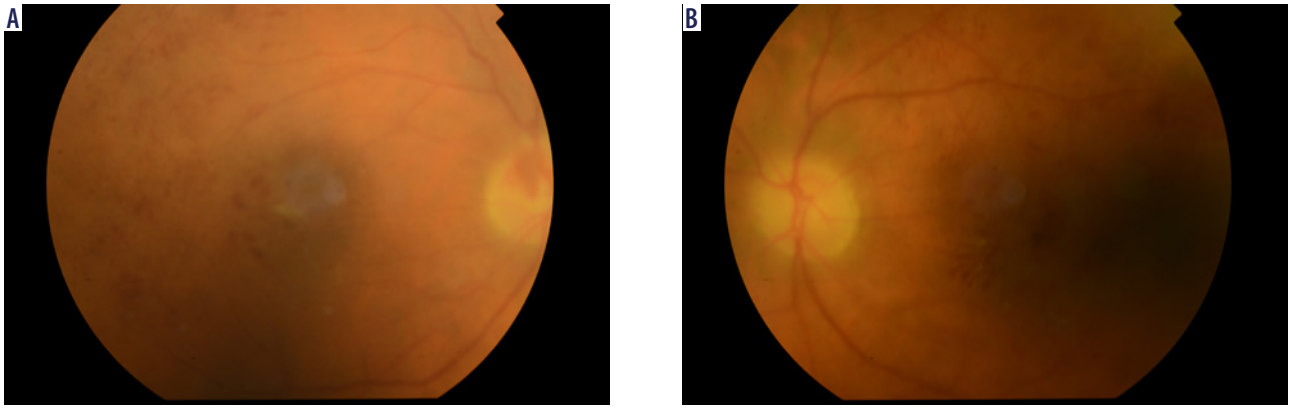

Figure 1. The fundus color photograph of the right (**A**) and the left (**B**) eye illustrates presence of retinal hemorrhages, aneurysmal dilatations, and retinal edema

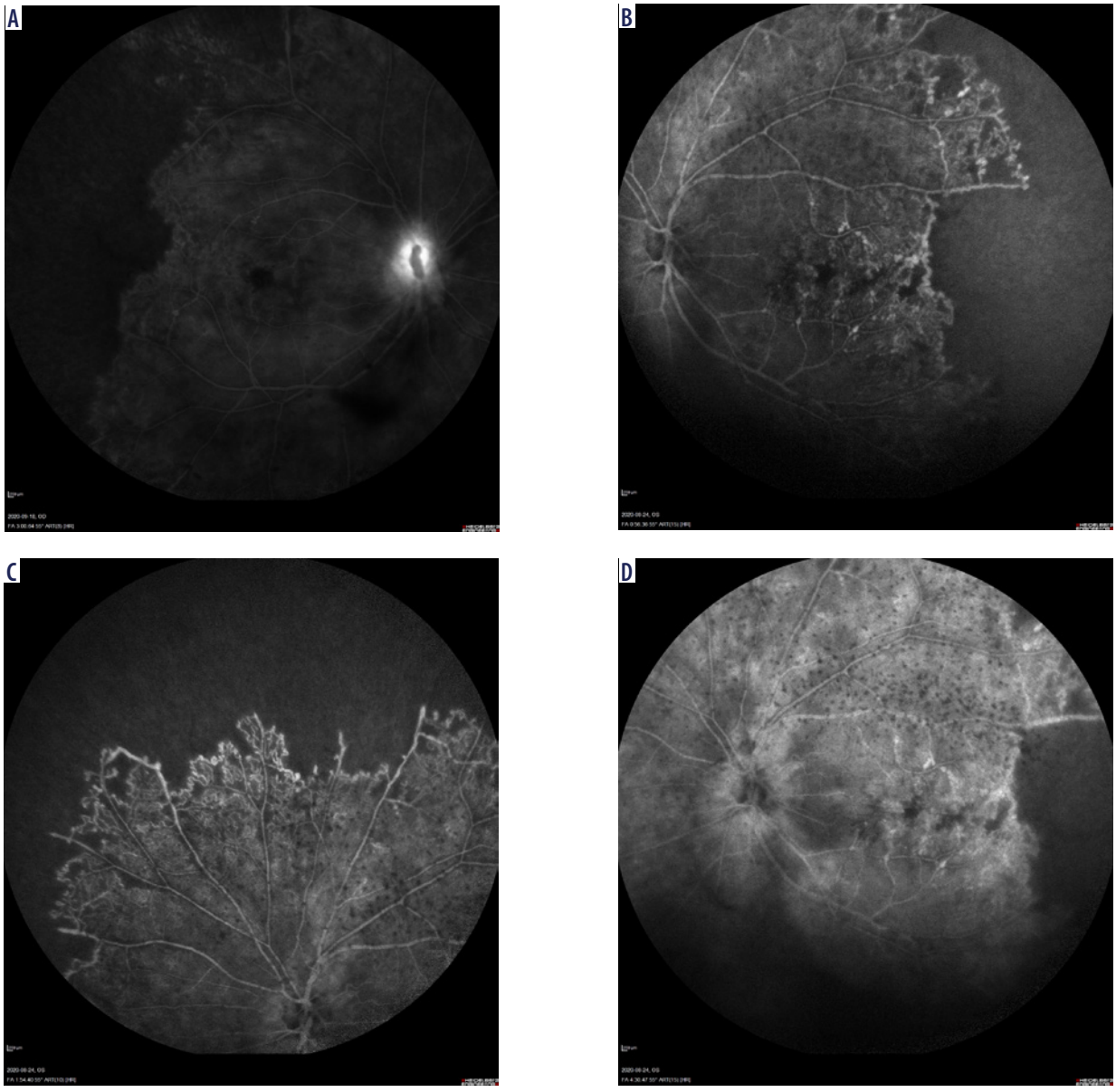

Figure 2. Fundus fluorescein angiography of the right (**A**) shows numerous saccular microaneurysms in the macula and middle peripheral area, extensive areas of non-perfusion, and leakage on the optic disc in the late phase. Fundus fluorescein angiography of the left eye (**B, C, D**) revealed numerous saccular microaneurysms in the macula and middle peripheral area, anastomoses, enhancement of the contrast, fluorescence blockage in the projection of hemorrhages, extensive areas of non-perfusion, and leakage on the optic disc in the late phase

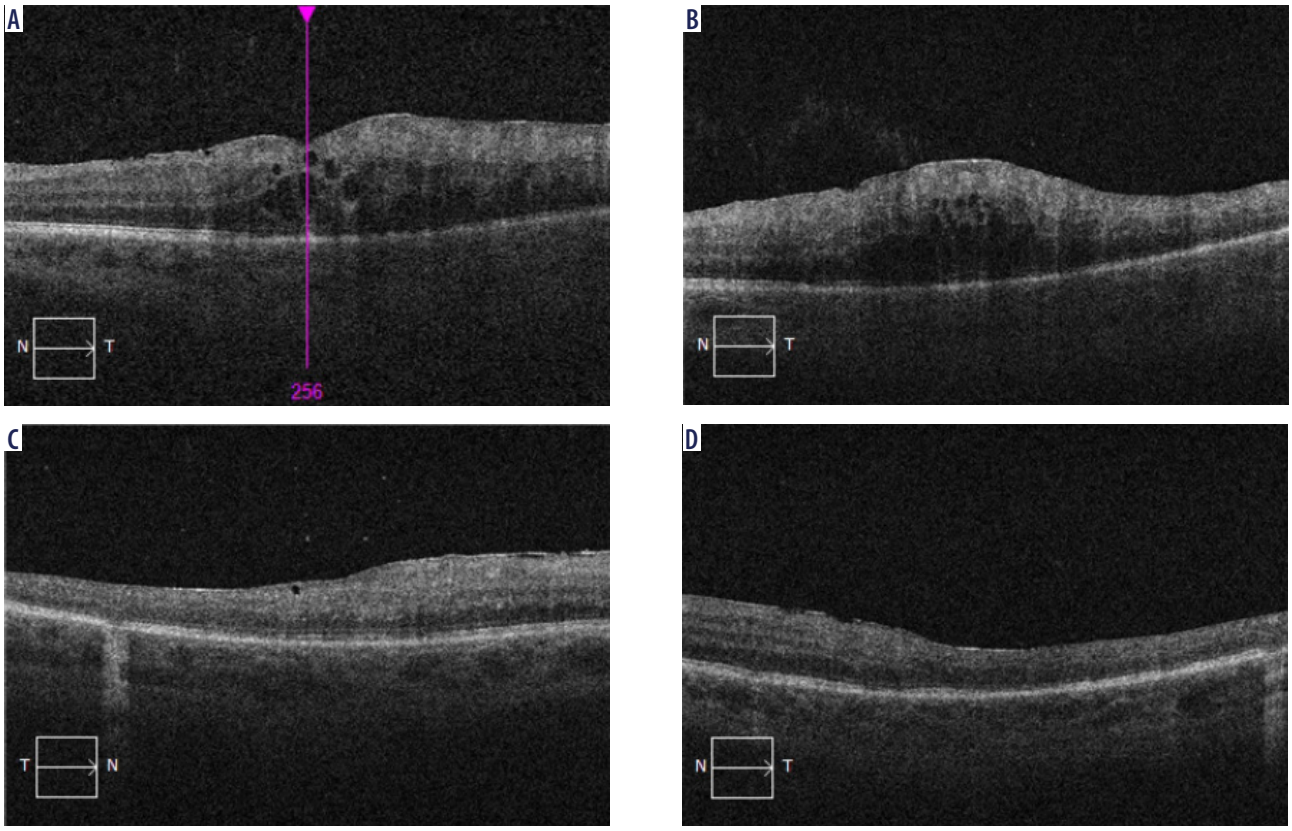

Figure 3. Macular OCT image of right (**A**) and left (**B**) eye demonstrates cystoid macular edema. OCT of right (**C**) and left (**D**) macula after intravitreal anit-VEGF injection reveals reduced macular thickness, but also increased deposition of exudates, atrophy of retinal neuroepithelium and epiretinal membrane

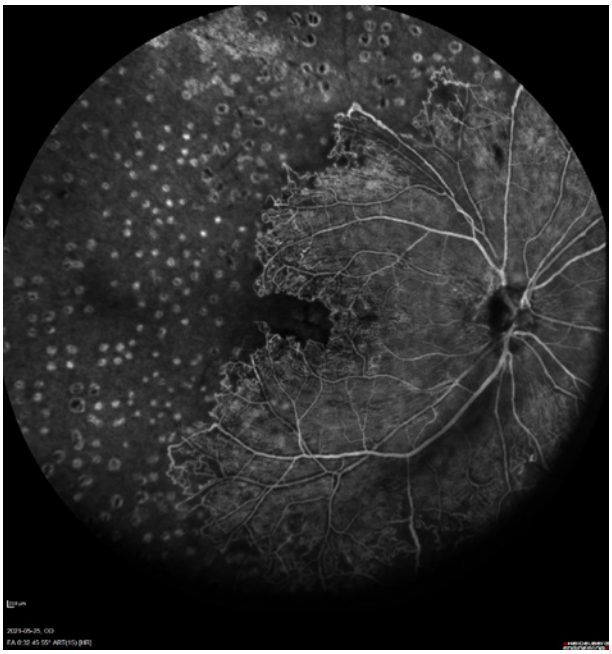

Figure 4. Fundus fluorescein angiography of the right eye after PRP: numerous saccular microaneurysms in the macula and middle peripheral area, anastomoses, enhancement of the contrast, extensive areas of non-perfusion, and peripheral scars after PRP

sound, which showed no abnormalities. Additional courses of PRP OU and grid photocoagulation in the LE were performed (Figure 4). The patient received another 2 anti-VEGF injections to each eye. 500 mg of mycophenolate mofetil per os twice daily was recommended. Best-corrected visual acuity remained 5/50 in the RE and 4/50 in the LE. The patient remains under regular follow-up.

DISCUSSION

Idiopathic retinal vasculitis, aneurysms and neuroretinitis syndrome is a type of retinal vasculitis, characterized by neuroretinitis and aneurysms, mainly distributed at the arterial junctions, due to turbulent blood flow [1]. The dynamic change in the number, shape, size and location of aneurysms could be explained by migratory inflammation process affecting alternate segments of vascular tree [5]. The abnormal blood flow might induce the capillary non-perfusion and cause an increase in VEGF, which is responsible for the neovascularization in the retina and optic nerve head, increased permeability of vessels, diffuse lipid deposition, persistent macular edema as well as vitreous hemorrhage [3, 4].

The use of imaging plays a major role in the diagnosis, monitoring of response to treatment and development of complications in IRVAN syndrome. The most revealing diagnosis examination is FFA, preferably by wide-field system, which

allowed recognition of aneurysmal dilatation and their leakage, diffuse optic nerve staining, areas of nonperfusion, retinal neovascularization, macular edema. Indocyanine green (ICG) angiography could show choroidal vascular abnormalities, which are not evident on FFA. Dilated and leaking choroidal vessels in the early to intermediate phase of ICG angiography may indicate an associated choroidal vasculitic component with vessel wall damage [6, 7]. The contribution of OCT is crucial in detecting vitreomacular traction and ERM. It also shows diffuse macular thickening, exudations or subretinal fluid. OCT angiography is an additional tool to FFA for visualization without the interference of dye leakage, which seems to be useful during longer clinical follow-up [6, 8].

There is no specific testing for IRVAN syndrome and diagnosis is based on the pattern of clinical and imaging findings with elimination of potential underlying systemic conditions. Systemic pathology is not usually identified, although some associations have been made with p-ANCA, antiphospholipid antibodies, raised homocysteine, sarcoidosis, tuberculin hypersensitivity and elevated intracranial pressure [9-13]. Since retinal and optic disc vasculature as well as choroidal circulation can be damaged in IRVAN syndrome, the differential diagnosis includes a range of inflammatory and infectious vascular entities; among others, Behcet's disease, sarcoidosis, multiple sclerosis, tuberculosis, syphilis and collagen vascular disorders. What is important, the presence of retinal vasculitis and peripheral nonperfusion makes Eales' disease a potential differential. However, this disorder typically affects younger male patients, is associated with positive tuberculin test, vestibuloauditory deficits and there is more predilection for the retinal veins [14].

In the presented case, the patient was found to have anti-DFS70 antibodies, which are commonly found in people who tested positive for ANA. Moreover, confirmation of their presence significantly reduces the likelihood of systemic rheumatic autoimmune diseases [15]. On the other hand, demonstrating positive IgM and IgG antibodies against Herpes virus in the described woman (although slightly above the norm) required taking into account the rare herpetic non-necrotizing retinopathy with occlusive retinal vasculitis and retinal neovascularization in the differential diagnosis [16].

The majority of studies support that an early PRP is the gold standard for ischemic retinopathy and a combined treatment with anti-VEGF is recommended in cases with neovascularization [2, 3, 17-20]. Macular grid photocoagulation can also be useful in the presence of macular exudation. There are other treatment options (trans-scleral cryotherapy, monoclonal antibodies, immunomodulatory therapy), but their impact on the course of the disease remains uncertain. Surgical management is reserved for end-stage disease where recurrent vitreous hemorrhage, tractional retinal detachment, vitreoretinal fibrovascular proliferation or ERM are present [2, 3].

Panretinal photocoagulation has been suggested as the treatment of choice when angiographic evidence of widespread retinal nonperfusion is present (fewer than two quadrants) [17]. Photocoagulation of the photoreceptors reduces the oxygen consumption of retinal pigment epithelium (RPE) and allows more oxygen to diffuse from the choroid to inner retina. The high rates of progressive neovascular complications despite laser photocoagulation of stage 3 patients and poor visual prognosis in stage 4 and 5 groups suggest that there is extreme difficulty in controlling the ischemic complications of the disease once neovascularization develops [2, 3]. This is also confirmed by description of the course of the disease and the treatment effects of our patient.

The use of intravitreal anti-VEGF in IRVAN syndrome has been documented in a few case reports for retinal neovascularization with favorable results for stages 3-5 [2, 18-20]. Immunosuppressive agents have been used to control retinal vasculitis and inflammation with satisfactory outcomes. However, it did not have any effect on peripheral non-perfusion areas, emphasizing the importance of combination therapy. Moreover, this treatment modality should be used carefully, as there is a risk of reactivation of opportunistic infections [21]. Steroid therapy has shown limited therapeutic response. However, resolution of macular edema and exudates as well as stabilization of the VA with a dexamethasone and fluocinolone acetonide vitreous implants have been shown [22, 23].

CONCLUSION

In summary, IRVAN syndrome is a rare retinal vascular disease that can progress rapidly to vision loss due to ischemic sequelae or massive exudation despite aggressive treatment. Early intervention with the use of laser treatment without waiting for neovascularization to develop is important, as the nature of the disease is more severe than other ischemic retinopathies. Anti-VEGF, immunosuppression and monoclonal antibodies have been used as adjunctive treatment to reduce disease progression. Careful long-term follow-up is recommended for all patients with this syndrome.

DISCLOSURE

The authors declare no conflict of interest.

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