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ROLE OF IMMUNOMODULATORY AND BIOLOGICAL THERAPY IN THE TREATMENT OF PATIENTS WITH BEHCET'S UVEITIS -CASES FROM CLINICAL PRACTICE

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Abstract

Morbus Behcet is a multisystemic, chronic disease, vasculitis, of unknown etiology. The highest incidence is in the countries of the so-called "silk road". In Macedonia, the frequency of this disease is currently unknown, but it is often under-diagnosed and unrecognized. In addition to the others, one of the main manifestations is ocular, which is presented by involvement of any of the structures of the uveal tract, the retina and the optic nerve.

The diagnosis is established on the basis of clinical parameters, complemented by genetic analyses-HLA-B51 typing and Pathergy positive test and ophthalmic imaging-techniques such as OCT, OCT-A, FFA. Treatment of the condition is multidisciplinary with local and systemic corticosteroid therapy, conventional immunosuppressive drugs, and biological therapy.

The aim of this paper is to present our experience in diagnosis and therapeutic modalities in patients with this disease.

***Keywords*:** uveitis, retinitis, Behcet's disease, azathioprine, cyclosporine, adalimumab

Introduction

Behcet's disease (Morbus Behcet) is a chronic multisystemic vasculitis of unknown origin. In the past known as the "silk road disease" described as far back as the writings of Hippocrates [1]. However, the first official reports of patients with this disease are mentioned in 1931 by the Greek ophthalmologist Adamantiades who described a patient with recurrent iritis, hypopyon, periphlebitis, arthritis and ulcers in the oral cavity and genitals [2]. Six years later, the Turkish dermatologist Behcet published three patients in whom the classic triad of oral and genital ulcers with recurrent iritis was present, giving the disease the name Adamantiades-Behcet, or today more commonly known as Behcet's disease [3]. The disease usually occurs between the second and fourth decade of life, although cases with onset in childhood or in older patients are encountered [4].

It affects both sexes equally, but in the case of the male sex, it is mainly with a more severe course, especially when it starts at a younger age. The incidence of the disease is different in different regions of the world, endemically highest in the countries of the so-called the Silk Road, that is, the Far and Middle East and the Mediterranean (Turkey, Iran, Iraq, Korea and Japan) [5].

The incidence in N. Macedonia is currently unknown, but it is often an underdiagnosed and missed disease, probably due to multisystemic manifestations and a different way of presentation.

Behçet's is a potentially fatal disease, with a mortality rate of 5% within 5-10 years of its diagnosis, mainly due to cardiovascular or neurological complications [6].

The disease is mostly sporadic, although several cases from the same family have been described, which still suggests a possible heredity with a currently unknown mode of inheritance. The most significant endogenous factor for the development of Behcet's is the HLA-B51 positive finding. Up to 80% of patients with this disease are HLA-B51 positive, and are at high risk for ocular manifestations. As Behçet's incidence is highest in Silk Road countries, it suggests a possible genetic cause or environmental influence [7].

The highest prevalence is observed in Turkey with 20-420:100,000 and Iran 80-100:100,000, in contrast to the Western world where it ranges between 0.3-7.5:100,000. Studies in France and Germany show that immigrants from countries with a high incidence of the disease have the same prevalence of the disease as in the countries from which they immigrated, suggesting a possible genetic cause rather than an environmental factor [8].

Shahram et al. in their study concluded that in the USA, immigrants from countries with high prevalence have a more severe clinical picture and multisystem involvement compared to patients from the mentioned countries [9]. This phenomenon is probably due to the fact that this disease is less often thought of in the Western world, as well as missing cases with a milder clinical picture, compared to Eastern countries, where the disease is quite common, so specialists from the respective fields have more experience in their timely treatment. recognition and treatment.

Today, the thesis of multifactorial etiopathogenesis of the disease is accepted. That is, genetic factors together with disturbed immune homeostasis, a tendency to autoimmunity and a possible infectious trigger factor are the basis of the pathophysiological mechanism. In recent years, it has been noted that the disruption of the oropharyngeal and intestinal microflora are correlated with this disease. Thus, Herpes simplex virus and several types of Streptococcus (especially Streptococcus sanguinis and Streptococcus pyogenes) play a possible role in the etypatogenesis of this vasculitis [10].

The diagnosis is made on a clinical basis, as there are no exact laboratory tests or pathognomonic findings. That is, the patient should meet certain clinical criteria, which differ from region to region of the world according to the specific characteristics of patients in that region. The most commonly used diagnostic criteria are those from the International Criteria for Behcet's Disease (ICBD), with the highest sensitivity and predictive value [11].

	ICBD Scoring System	**ISG Scoring System**	**Japanese Scoring System**
Oral ulcer	*2 point*	*Mandatory*	*Major criterion*
Genital ulcer	*2 point*	*Minor criterion*	*Major criterion*
Skin region	*1 point*	*Minor criterion*	*Major criterion*
Uveitis	*2 point*	*Minor criterion*	*Major criterion*
Pathergy test	*1 point*	*Minor criterion*	*Not included*
Arthritis	*Not included*	*Not included*	*Minor criterion*
Epididymtis	*Not included*	*Not included*	*Minor criterion*
GIT	*Not included*	*Not included*	*Minor criterion*
Neurological	*1 point*	*Not included*	*Minor criterion*
Vascular	*1 point*	*Not included*	*Minor criterion*

Table 1: Comparison between: ICBD (International Criteria for Behcet's Disease), ISG (international Study Group) [12] and Japanese Scoring System diagnostic criteria. ICBD requires ≥4 points, ISG 3 out of 5 components with Oral ulcer being mandatory, Japanese scoring system requires 3 major or uveitis and one major and two minor criteria. Adapted from Kirino and Nakajima [13]

The Pathergy test is not included as a diagnostic criterion in the Japanese Scoring System, because it is often negative in patients with Behçet in Japan, in contrast to Mediterranean countries where it is quite often positive when testing patients suspected of this disease, in even over 40% of the cases.

HLA-B51 positive finding, although not included as a diagnostic criterion, is of great importance in establishing the diagnosis [11].

Case 1.

In November 2022, a 21-year-old patient came to the PHI UC for eye diseases in Skopje with a sudden decrease in the vision of the right eye, which happened one day before the examination. He gave a

history of similar such events in both eyes, several times previously in the past two years, and was treated by another ophthalmologist as anterior uveitis.

Occasionally there was an improvement in the condition, but the remission did not last long. He denied other illnesses and conditions, but during targeted questions we noticed that on several occasions in the past years white sores appeared in his mouth, and on his genitals that lasted one to two weeks and disappeared by themselves, they were painful and were a frequent problem for him, but he did not mentioned them to a medical person. At the time of examination, several aphthous changes were present in the patient's oral cavity.

The best corrected visual acuity (BCVA) of the affected eye was: counting fingers in front of the eye, while on the left it was 0.5. Both intraocular pressures were within normal limits. During the ophthalmological examination of the anterior segment of the eye, it was observed: pronounced ciliary hyperemia, transparent cornea with cellularity in the anterior chamber of 4+ and the presence of a 3mm mobile hypopyon, the transparency of the chamber was moderately reduced, with flare 1+, reaction of the pupil to light it was weakened, and cellularity and haze of 3+ was observed in the anterior vitreous. Fundoscopic examination of the right eye was impossible. The clinical findings of the left eye were stable, the anterior segment without active inflammation, with a few pigmented precipitates on the anterior capsule of Lens crystallina, and degenerative membranous changes in the anterior vitreous, the result of previous inflammation. The funduscopic finding of the left eye indicated a previous event of the same, with the presence of a thin epiretinal membrane in the macular region, and several blot hemorrhages in resorption nasally from a papilla with a single occluded-anemic arterial blood vessel in the upper nasal arcade. Sonographic finding of the right eye showed marked exudation in the vitreous, which was ablated from the posterior attachment and edematous thickening of the retina, the left eye also with ablated vitreous and sparse cellularity accompanied by degenerative membranous changes. According to the clinical characteristics and the anamnestic data, a diagnosis of Panuveitis of the right eye was made, assuming Behcet's disease.

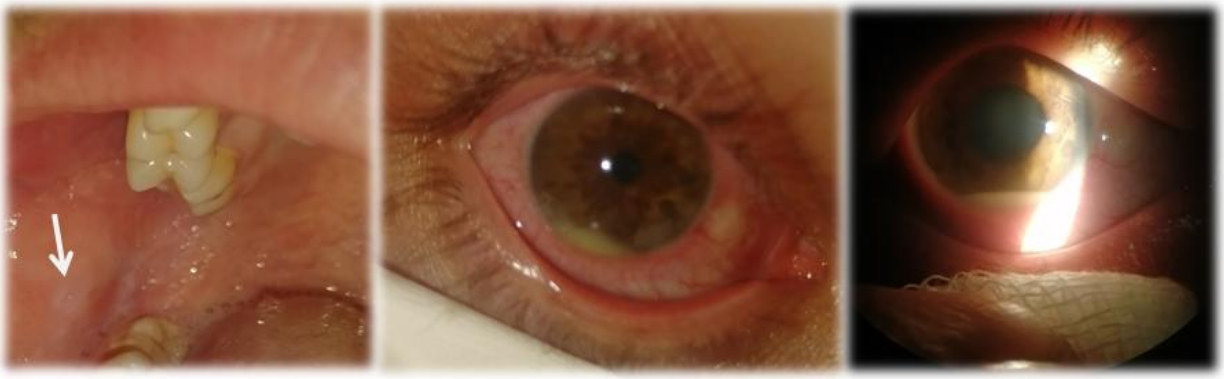

Figure 1. Aphthous changes in the oral cavity (arrow), ciliary hyperemia, hypopyon and cellularity in the anterior chamber of the eye

The patient was hospitalized at PHI UC for eye diseases in Skopje, in consultation with a rheumatologist, a Pathergy test was performed, it was positive, laboratory parameters indicated elevated sedimentation and CRP, and ANA, ANCA, RF, CCP, SSA, SSB were normal. Serum tests for HSV, VZV, CMV, Toxoplasma gondii, HIV, Hepatitis B and C, quantiFERON-TB Gold test were negative. HLA typing for B51 was positive.

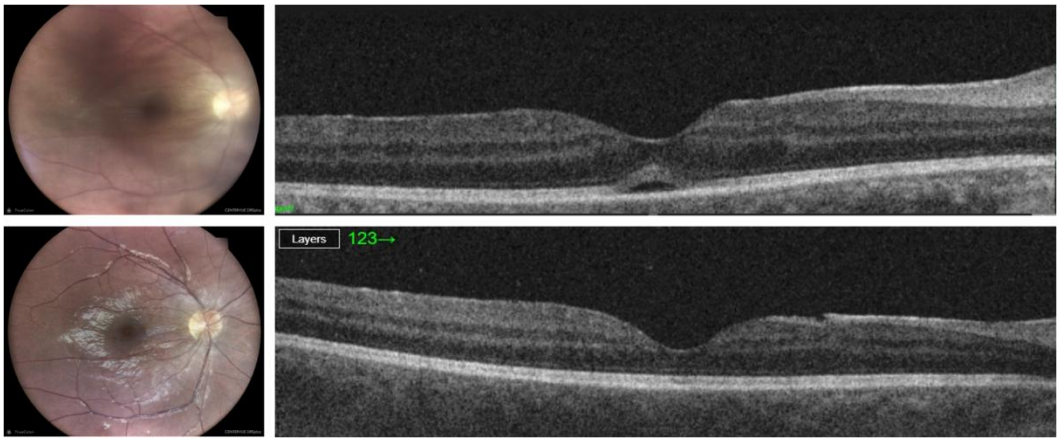

Figure 2. Vitritis present, haze 2+, with small subretinal fluid in the fovea, top, reduced vitritis, epiretinal membrane present, and changes in foveolar depression after pulse methylprednisolone regimen, bottom

According to the clinical and laboratory investigations, a diagnosis of Behcet's disease with ophthalmological manifestations - panuveitis was made. The patient was placed on a intravenous pulse methylprednisolone regimen of 500 mg/day for 3 days, and then continued with Prednisolone tablets 1.5 mg/Kg/day with a gradual dose reduction in the following period to 5 mg/day as a maintenance dose. Next, immunosuppressive therapy was started, Azathioprine tablets in a dose of 2mg/Kg/day. Corticosteroid therapy in the form of drops and topical mydriatics and cycloplegics were applied locally. Over the following weeks, the marked vitritis of the right eye gradually resolved, visual acuity improved to 0.3, and inflammatory retinal infiltrates, retinal hemorrhage, and macular edema were noted on funduscopic examination.

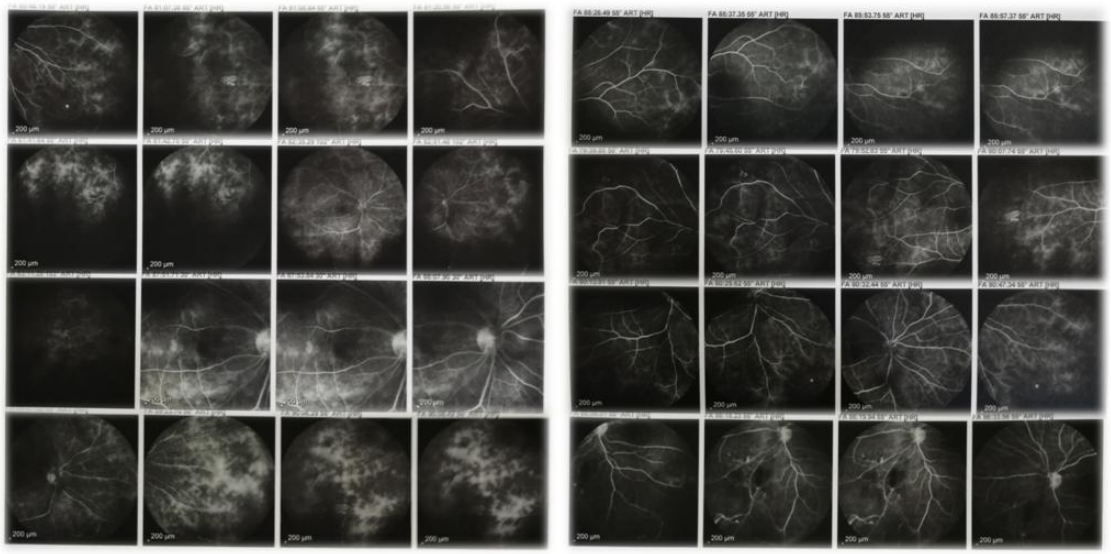

Figure 3. Fluorescein angiography of the right and left eye, respectively. Vascular leakage, areas of hypoperfusion, in the late stages of the angiogram leakage from vessels, fern-like, active retinal vasculitis.

In the following three months, the clinical condition improved significantly with visual acuity of 0.7, complete resorption of macular edema, reduction of retinal infiltrates and hemorrhages. A fluorescein angiography (FAG) was performed, which showed subclinical vasculitis activity, that is, zones of vascular leakage, which intensified in the late stages of the angiogram with a fern-like appearance, accompanied by local zones of hypoperfusion, this finding was bilateral, more pronounced on the right

eye. Due to angiographically visible disease activity despite the absence of clinically manifest disease, in consultation with a rheumatologist the patient was placed on additional therapy, a biological agent - Adalimumab, a human monoclonal antibody against TNF-alpha, with subcutaneous administration of 40 mg every other week. At the next angiogram, 3 months after the placement of Adalimumab, the patient has a significant regression of the angiogram and no relapses of the disease, which has maintained a remission of the disease for 10 months until the moment of publication of this paper.

The patient is regularly monitored by an ophthalmologist and a rheumatologist, with control biochemical analyzes every 2 months, so far without side effects from the applied therapy and visual acuity at the last control of 0.9 bilaterally.

Case 2.

A 39-year-old patient came for an examination at the PHI UC for eye diseases in Skopje, October 2022, with pronounced redness of the right eye and slight blurring of vision. During the anamnestic evaluation, the patient denied other diseases and conditions, gave information about the appearance of small painful sores in the area of the mouth for the past few years. During the ophthalmological examination, the best-corrected visual acuity was 0.8 in the affected eye and 1.0 in the other. Tonometry, on both sides, was within normal values. During a biomicroscopic examination of the anterior segment of the right eye, marked ciliary hyperemia was observed, with cellularity in the anterior chamber 2+, and a mobile hypopyon of 2 mm, the pupil properly reacts to light, the biomicroscopic findings of the left eye were normal. The fundoscopic finding of the right eye showed a single retinal infiltrate nasally from the papilla, with several dot-blot hemorrhages - suspicious for retinal vasculitis, the left eye without pathological findings. Echographic and OCT analyses, on both sides, without changes. Corticosteroid and cycloplegic topical therapy was prescribed locally and hospitalization was advised. Due to the clinical characteristics of uveitis and the obtained anamnestic data, the patient was also referred for a consultative examination by a rheumatologist, HLA typing and biochemical-laboratory analyses. However, due to his carelessness and subjective improvement of vision, the patient refused hospitalization, did not perform the assigned analyzes and did not appear for a control ophthalmological examination.

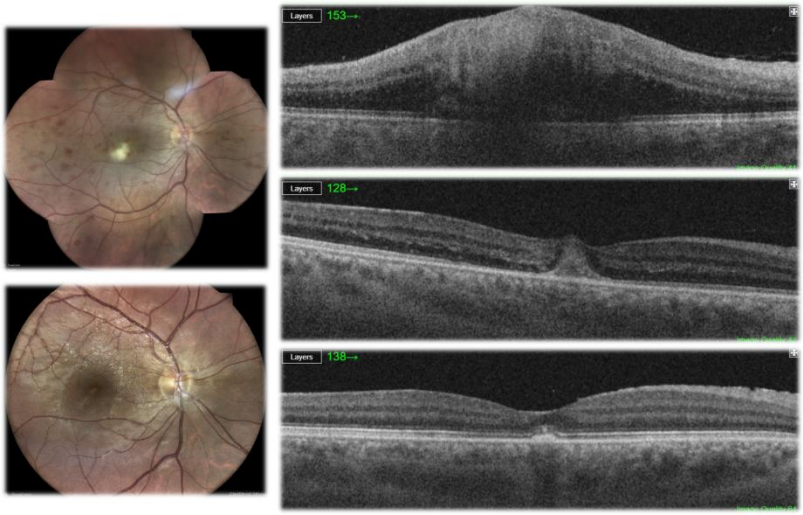

Figure 4. Fundus photographs and OCT slide sections: Active retinal vasculitis, with infiltrate and edema in the macula, images above, gradual resolution of the finding and improvement of morphological features, images below, right eye

Three months later, the patient returned to the PHI UC for eye diseases in Skopje, with a worsening clinical condition. That is, the best-corrected visual acuity of the right eye was hand movement in front of the eye, with moderate bulbar hypotonia. When examining the anterior segment of the affected eye, moderate hyperemia, cellularity in the anterior chamber of 4+, flare of 2+, without the presence of hypoion was observed. During the fundoscopic examination in the lower vitreous, several oval infiltrates similar to a pearl necklace were observed preretinally, numerous dot-blot hemorrhages paravasally in all sectors of the fundus, pronounced edema in the macula with retinal oval infiltrate immediately to the foveolar region, signs of active retinitis. The patient was hospitalized at PHI UC for eye diseases in Skopje, ultrasound and OCT imaging analyses, laboratory tests were performed, infectious agents were ruled out, Pathergy test and HLA-B51 typing were performed in consultation with a rheumatologist, all positive, which led to the diagnosis of Behçet's disease. with retinal vasculitis. The patient was prescribed an initial dose of methylprednisolone of 500 mg/day for three days, and then continued with oral Prednisolone 1.5 mg/Kg/day with a gradual dose reduction in the following period, supplemented with immunosuppressive therapy - Azathioprine 2.5 mg/Kg/day. As well as Cyclosporin-A tablets 3mg/Kg/day due to pronounced retinal vasculitis. Systemic therapy was supplemented with local topical corticosteroid and cycloplegic therapy. In the following weeks, there was a regression of the findings: retreat of the retinal hemorrhages, infiltrate and macular edema, retreat of the cellularity in the anterior chamber and of course improvement of the visual acuity, i.e. 0.4. Three months after starting treatment, the patient underwent fluorescein angiography, which showed no vasculitis activity.

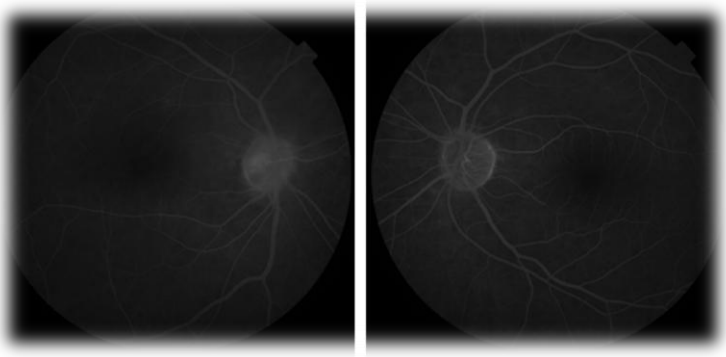

Figure 5. Fluorescein angiography after placing the patient on systemic immunosuppressive therapy. There are no vascular signs of active vasculitis, moderate hyperfluorescence at the level of the papilla is observed in the right eye.

The patient is regularly monitored by an ophthalmologist and a rheumatologist, without signs of relapse of the disease or side effects of the systemic immunosuppressive therapy, in the past 8 months. The visual acuity of the last control is 0.8 in the right eye and 1.0 in the left.

Case 3.

A 54-year-old female patient with reduced vision in the right eye came for an examination at PHI UC for eye diseases in Skopje, in January, 2023. The best-corrected visual acuity of the right eye was 0.08, while that of the left eye was 0.8. Tonometric parameters normal on both sides. During the biomicroscopic examination of the right eye, the presence of 1+ cells in the anterior chamber, a single old synechiae at 5h, as well as cellularity and haze in the vitreous was noted. During the fundoscopic examination, in the lower parts of the vitreous, several condensed inflammatory deposits were present preretinally, as well as edema in the macula, the left eye without pathological findings. Posterior segment OCT and echography were performed. From the anamnestic data, we learned that the patient had reduced visual acuity several months ago, without other comorbidities, but during targeted questions, we received information that in the past years, sores appeared constantly in the oral cavity, as well as slightly elevated erythematous changes on the lower extremities. In order to rule out possible late-onset Behçet, the patient

was sent for HLA B51 typing, Pathergy testing, extensive laboratory and serological analyses. Results indicated HLA B51 and Pathergy positive results, other tests and chest X-ray were normal, including the quantiFERON-TB Gold test.

The patient was diagnosed with Behcet's disease, with ophthalmological manifestations and late onset.

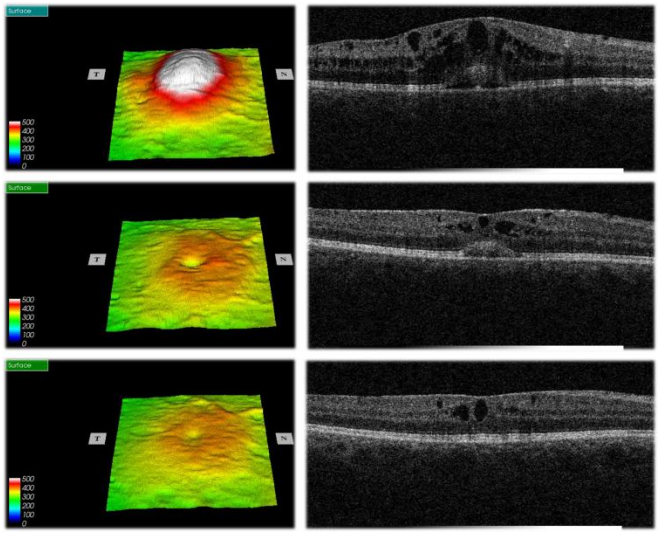

Figure 6. Reduction of cystoid macular edema over time under the influence of local and systemic therapy, OCT and macular topography of the right eye

In order to reduce the vitritis and marked cystoid edema in the macula, she is prescribed systemic corticosteroid therapy - Prednisolone 1.5 mg/Kg/day with a gradual dose reduction in the following period to 5 mg/day as a maintenance dose and immunosuppressant - Azathioprine tablets 2.5 mg/Kg/day. A dose of Triamcinolone acetonide was applied in the subtenon space and the same was repeated three more times at a distance of one month from one application to the next, for the withdrawal of macular edema. Local topical corticosteroid and cycloplegic therapy was applied in the first weeks after diagnosis. In the subsequent follow-up period, there was a significant reduction of cystoid macular edema, without the appearance of new ulcerations in the mouth, and an improvement in visual acuity. At the last check-up, 8 months after the start of therapy, the best-corrected visual acuity of the right eye was 0.8. Fluorescein

angiography during the entire period was without pathological changes, at the last control, slight residual edema was present in the macula, with an epiretinal membrane and degenerative cystic intraretinal changes.

The patient is regularly monitored by an ophthalmologist and a rheumatologist, so far without side effects from systemic and local therapy.

Discussion

One of the main manifestations of this disease is an affection of the intraocular structures - uveitis. Although it can be presented as exclusively anterior, mainly in females, or posterior, the majority of patients have panuveitis.

By definition Morbus Behcet is chronic bilateral relapsing nongranulomatous panuveitis with retinal vasculitis. The anterior segment of the eye mainly has light to moderate ciliary hyperemia, serous exudation in the anterior chamber, fibrin components are mostly absent, due to which the formed hypopyon is mobile and quite light colored. Cellularity in the anterior chamber (CA) can be pronounced, without the presence of precipitates, and with the moderate flare persisting for a long period. Hypopyon is a poor prognostic sign for the course of the disease, it occurs in about one third of the patients [14].

In our case, both male patients had CA exudation with mobile hypopyon present and cellularity of 3+ or 4+, and CA flare, 1+ to 2+. Both patients had bad clinical findings and visual acuity compared to the third patient who had a significantly reduced clinical picture of the anterior segment of the eye. Vitritis is a common finding in patients with Behcet's panuveitis. At the beginning of the attack, it is accompanied by numerous cellularity and haze of the vitreous, so visualization of the fundus is often impossible, haze under therapy, but it also decreases spontaneously in the next few days, with which the visual acuity gradually improves [8].

A major feature, present in one of our patients (case 2), is the presence of small preretinal precipitates in the lower vitreous arranged like a pearl necklace that appear towards the end of the first week of the inflammatory process and persist for several weeks afterwards. One of the main causes of a significant decrease in visual acuity that can persist for weeks and months after the initial inflammatory attack is cystoid macular edema (CME). CME is due to the impaired blood-retinal barrier of the small blood vessels in the perifoveolar region. It occurs in about 2/3 of Behcet's patients [15].

All three patients presented to us had a certain degree of CME, in case 3 it was quite accentuated, with a chronic course and a subtenon application of corticosteroid was necessary to withdraw it. At the time of publication of this paper, her CME is significantly reduced, but still exists with subsequent intraretinal cystic changes. CME in case 1 responded very effectively to the overall systemic and local therapy, during the follow-up there was a subclinical leakage from the small blood vessels, which significantly improved after the application of a biological therapeutic agent - Adalidumab.

A characteristic of this disease is the presence of occlusive necrotizing retinal vasculitis, presented with periphlebitis and periaortitis as well as bilateral thrombosis of blood vessels, with subsequent hypoxia of the affected retinal tissue and possible neovascularization and retinal hemorrhages. After the acute inflammatory process, the affected blood vessels undergo attenuation and emptying of the contents due to which they are called ghost vessels [16].

In case 1 of the presented patients, even during the initial examination of the left eye, such a vessel was observed nasally from a papilla from a previous unexamined vasculitis of that eye. Untreated patients in the final stage of the disease end up with a pale papilla, numerous empty blood vessels - ghost vessels, thinned ischemic retina and gliosis that differentially resembles a patient in the final stage of retinitis pigmentosa.

Regarding the systemic manifestations of the disease, aphthous oral lesions are most often present, which are present in almost all patients, which was also the case in ours. These are oval, painful ulcerations up to 1.5 cm in size that appear several times during a year, disappear in one to two weeks without leaving scars. In contrast, ulcerations of the genital region (scrotum and labia), also painful, leave scars after their spontaneous healing, present in case 1. Ulcers can also be seen in the esophagus, stomach, or small intestine in association with intestinal Behcet. The most common skin change is Erythema nodosum - elevated pinkish efflorescences that appear on the extremities and upper body, papulopustular and folliculitis-like lesions are also encountered [17].

Case 3 in our case had the presence of Erythema nodosum on the lower limbs. Half of the patients have some type of arthritis, usually monoarticular, which lasts for several weeks. Since the basis of the disease is vasculitis, patients may have a systemic affection of arterial and venous blood vessels that presents as thrombophlebitis, venous thrombosis, occlusive syndrome or aneurysmal dilatations. The most common cause of death is pulmonary artery aneurysm. Other complications can be pericarditis, myocarditis or endocarditis, myocardial fibrosis, etc. In 5-10%, a neurological manifestation of the disease occurs, with lesions in the white brain mass and brain stem as well as vascular changes (occlusions and thrombosis), papillitis, papilloedema or cranial nerve paralysis [6].

From the investigations we did and the anamnestic data we received from the three patients, as well as during the overall follow-up, no other possible systemic involvement appeared.

The ophthalmological evaluation and diagnosis of the disease includes a multimodal approach that, in addition to the standard clinical examination, also includes modern imaging methods, especially for the evaluation of the posterior segment of the eye.

SD-OCT is an indispensable tool for exact examination of the maculopapillary region, showing retinal infiltrates, CME, possible RNFL affection in the peripapillary region, etc. Through it, the entire cytoarchitectonics of both the retinal tissue and the subretinal choroid is analyzed. Choroidal thickening occurs quite often in Behcet's patients. The retinal pigment epithelium (RPE) is usually not affected.

Retinal infiltrates present as hyper-reflective thickenings in the inner layers of the retina, which gradually disappear without leaving any scars. Ganglion cells complex (GCC) in the macular region also undergo changes during the acute attack and post-inflammatory, as a consequence of the ischemic event [18].

A reduction in GCC was also observed in our patients 1 and 2 after the patients entered remission. CME and also the central avascular zone are affected in Behçet's patients. That is, as we emphasized before, due to disruption of the blood-retinal barrier, there is a leakage of fluid from the perifoveal blood vessels and the formation of CME, which can have a chronic course and be the cause of vision reduction [15].

OCT-A in patients after an attack of Behchest's uveitis shows a reduction in the density of capillary blood vessels with an increased foveal avascular zone (FAZ) [19].

Fluorescein angiography (FFA) is the gold standard in the follow-up of patients with Behçet's retinitis, both in terms of their diagnosis and in the overall evaluation of the state of vasculitis in the retinal circulation. Through FFA, zones of hypoperfusion, as well as zones of leakage from blood vessels at the level of peripheral parts of the retina, fundus and papilla, are observed [20].

According to the overall evaluation of the FFA, an assessment is given of disease activity even when the clinical parameters suggest that the patient is in remission, as in case number 1, but also of the severity of the vasculitis. Today, there is the possibility of an ultra-wide field imaging system that provides up to 200° view of the retina, which enables a panoramic view of the entire retinal condition. All three of our cases were regularly followed up with the necessary imaging techniques at our clinic during the past year. Additional diagnostic modalities that today find application for monitoring patients with Behçet's uveitis are: indocyanine green angiography (ICG), evoked visual potentials (VEP), laser flare-cell photometry, as well as anterior segment OCT with pachymetry, specular microscopy, etc [8].

Considering that the disease affects all three parts of the uveal tract, the following are considered as differential diagnoses: infectious causes of uveitis (toxoplasmosis, syphilis, tuberculosis, CMV), sarcoidosis, intraocular lymphomas and HLA-B27 associated anterior uveitis [21].

However, with adequate anamnestic data and extensive laboratory and imaging analyses, this disease can be distinguished from the previously mentioned ones.

Treatment of patients with Behçet's is multidisciplinary, depending on the overall systemic manifestations.

Ophthalmological treatment is mainly aimed at the posterior segment of the eye because its changes are of crucial importance on the prognosis of visual function. In patients with exclusively anterior uveitis, application of local topical corticosteroid therapy supplemented with cycloplegic and mydriatic topical therapy for a period of one to two months achieves a satisfactory effect on the control of ocular inflammation. In contrast, patients with acute posterior uveitis or panuveitis require more aggressive systemic treatment to prevent serious irreversible visual impairment. Initially, patients, as in our cases 1 and 2, start with pulse doses of methylprednisolone administered intravenously (250-1000mg/day) for up to three days, and then continue with oral corticosteroid therapy at a dose of 1-1.5mg/ kg/day. It is important to note that systemic corticosteroid preparations should be used together with immunosuppressive drugs, because independent corticosteroid therapy does not achieve long-term remissions in the patient and is a risk factor for a poor prognosis in the long term [22].

In patients with chronic or pronounced CME, the application of local (subtenon and intravitreal) corticosteroids is also considered. Such an example is case 3, a patient with pronounced and chronic CME in whom subtenon injection of corticosteroid was applied on several occasions.

For the time being, immunosuppressive drugs have a main place in the treatment of Behcet's uveitis. Azathioprine and Cyclosporin-A are the drugs with the highest recommendation according to EULAR [23]. Azathioprine is prescribed orally in doses of 2-2.5mg/Kg/day with monitoring of liver

enzymes at the three-month level and blood count, due to the potential myelosuppressive effect of the drug and hepatotoxicity. Cyclosporin A is contraindicated in patients with neuro-Behçet's disease. It can be prescribed alone or in combination with Azathioprine or biological therapy. Therapeutic doses of this drug are 2.5-5mg/Kg/day. In addition to these two immunosuppressive drugs, the use of cyclophosphamide, methotrexate and mycophenolate mofetil as alternative therapeutic drugs has also been described in clinical practice [23,24]. In the last decade, biologics have gained increasing use in the treatment of a number of posterior uveitis and panuveitis, including Behçet's. Since the basis of the disease is non-infectious, immune-mediated vasculitis, where TNF-alpha is one of the main pro-inflammatory molecules in the pathogenetic mechanism, the use of TNF-alpha inhibitors is logical. Two preparations are mainly used - Adalidumab and Infliximab. According to current recommendations, they are used as second-line treatment, when conventional immunosuppressant will not provide complete remission of vasculitis, as in our Case 1. However, today there are also recommendations for the use of these agents as first-line treatment in active aggressive Behçet's uveitis. Administration of Infliximab is intravenous at a dose of 3-5mg/Kg at 0, 2 and 6 weeks and then maintenance doses every 4-8 weeks depending on clinical and angiographic characteristics. Minimal treatment with this agent lasts for 12 months, with remission of the ophthalmic finding of 3-6 months, when the gradual withdrawal of the agent can be started. Gives positive effects: improvement of visual acuity, reduction of the frequency of ocular attacks and retinal vasculitis with reduction of CME [25].

Adalidumab is currently the only non-corticosteroid agent approved by the FDA for the treatment of non-infectious intermediate, posterior and panuveitis. The application of this drug is subcutaneous in a dose of 40 mg every other week. 2/3 of the patients who use this drug have a withdrawal of the angiographic characteristics of active vasculitis after three months, and even over 90% achieve this after 12 months of application [26].

The use of anti-TNF-A as a first-line treatment is justified in severe cases of Behcet's uveitis. They can be combined with conventional immunosuppressants, but more recent studies have shown that their independent administration has the same effect as the combination [23].

Patients should be screened for potential tuberculosis, demyelinating, or malignancies before undergoing these therapeutic modalities.

In addition to TNF-A, interferon-A (especially for refractory neuro-Behcet), tocilizumab, golimumab, anakinra, rituximab and others are recommended as second-line biological therapy in the world for this condition [8,14]. Additional studies in the future are necessary to establish the efficacy and potential side effects of the use of these drugs in the treatment of patients with Behçet's uveitis.

Conclusion

Through this paper, we tried to review the current attitudes and guidelines in the treatment of patients with Behçe's uveitis, as well as to present our experience in the treatment of patients with this inflammation, applying different therapeutic modalities based on the morpho-functional characteristics and age of the patients. It should be emphasized that Behcet's disease is not so rare, but quite often underdiagnosed in our country. A multidisciplinary approach is necessary for the proper monitoring and management of patients in order to preserve visual function and overall health.

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