ACUTE RETINAL NECROSIS IN A PATIENT WITH LEUKOPENIA AND FOLLICULAR NON-HODGKIN LYMPHOMA IN REMISSION

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Abstract: Acute retinal necrosis is a rare ophthalmic condition characterized by diffuse uveitis, retinal vasculitis, and subsequent retinal necrosis. It can occur in both immunocompetent and immunocompromised patients, with no gender or age predispositions. Etiologically, it is most often caused by the Varicella Zoster and Herpes Simplex viruses, however, cases have been described where Cytomegalovirus and Epstein-Barr virus are the causes of this condition. Bilateral affection is found in more than 1/3 of cases and is even higher in immunocompromised patients. The diagnosis is made clinically, and the etiological agent can be confirmed by polymerase chain reaction (PCR). Treatment is based on systemic antiviral therapy, primarily Acyclovir, followed by corticosteroid therapy and Aspirin.
The aim of this paper is to present a case of acute retinal necrosis, a rare ophthalmic manifestation in a patient with leukopenia due to chemo-immunotherapy for the treatment of follicular non-Hodgkin's lymphoma.
A 62-year-old female patient was sent to PHI University Clinic for eye diseases in Skopje by a hematologist due to a decrease in vision first in the right and then in the left eye in the past two weeks. For several years, the patient has been treated by a hematologist for follicular non-Hodgkin's lymphoma. Immediately before the ophthalmological event, the patient had leukopenia as a result of the last cycle with chemo-immunotherapy. The best-corrected visual acuity at the initial examination of the right eye was 0.4; and on the left 0.6. Using biomicroscopic and funduscopic findings accompanied by echographic features and fluorescein angiography of the posterior segment, a working diagnosis of acute retinal necrosis was made and confirmed by viral serology and PCR from vitreous punctate. Varicella Zoster virus was isolated as the cause of retinal vasculitis and necrosis. Appropriate systemic antiviral, corticosteroid therapy and Aspirin were applied to the patient for several months. In addition, postischemic retinal areas were barraged to prevent possible retinal ablation, with laser photocoagulation. During the investigation, there was a gradual improvement in visual acuity, which at the last examination was 0.6 on the right eye; 0.9 on the left eye, respectively.
Timely diagnosis and appropriate treatment in patients with this ophthalmic condition, especially when it is presented in an immunocompromised patient, is of crucial importance for preserving visual function and preventing numerous ophthalmic and systemic complications.
Keywords: retinitis, varicella zoster virus, panuveitis, retinal necrosis, leukopenia, lymphoma.

1. INTRODUCTION

Acute retinal necrosis (ARN) is a fulminant viral necrotizing retinitis that can occur in both immunocompetent and immunocompromised patients, regardless of gender and race. Mainly in people between the fifth and seventh decade of life. It was first described in 1971 by Urayama (Urayama, 1971), and a viral etiology was first demonstrated in 1982 by Culberston et al. in enucleated eyes using electron microscopy (Culbertson, 1982). In the years that followed, the different viral genesis of the disease was demonstrated with several techniques. Varicella Zoster (VZV), Herpes Simplex type 1 and 2 (HSV) are the most common etiogenic factors, however, cases of Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) have also been described as causes of ARN (Bergstrom & Tripathy, 2023).
The patient's genetic background is also thought to play a role in the pathogenesis of this disease. Individuals who are HLA-DQw7, HLA-Bw62, and HLA-DR4 positive in the USA, or HLA-Aw33, HLA-B44, and HLA-DRw6 in Japan are at higher risk of this disease (Holland et al., 1989). The patient's immunological condition: immunocompromised due to corticosteroid therapy, HIV infection and other chronic diseases are mentioned as possible risk factors for the occurrence of ARN (Batisse et al., 1996).

2. CASE REPORT

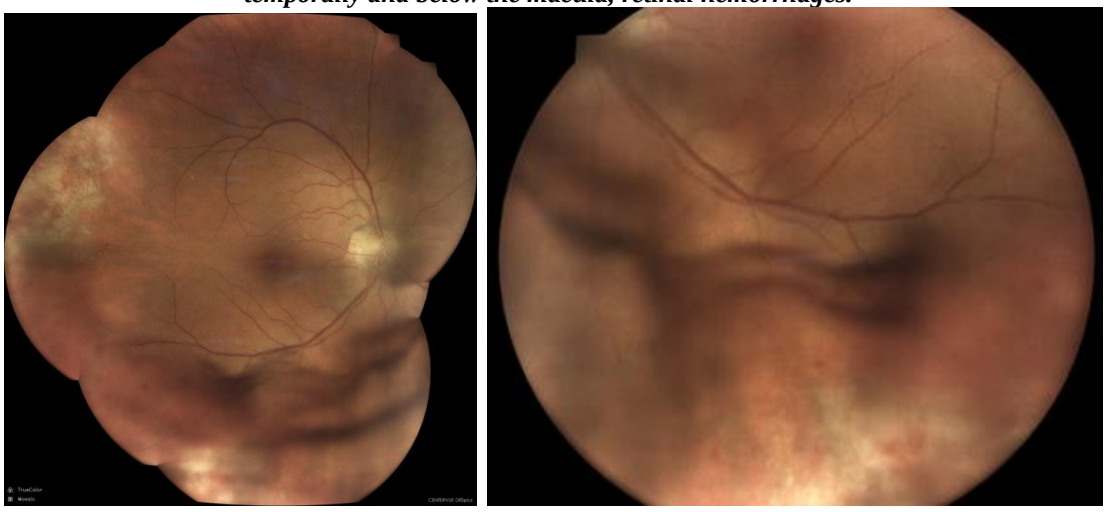
A 62-year-old female patient was sent to PHI UC for Eye Diseases-Skopje by a hematologist for an ophthalmological evaluation due to vision impairment, especially in the right eye, which occurred in the past two

weeks. From the anamnestic data, we found that it is a patient with follicular non-Hodgkin's lymphoma who has been examined and treated by a hematologist for 7 years with appropriate chemo-immunotherapy, with several relapses of the disease, but with sustained remission in the last six months, both clinically and according to PET/CT analyses. The patient completed the chemo-immunotherapy cycle with Obinutuzumab-bendamustine preparations two months before the appearance of vision changes. As a consequence of the suppressive effect of this protocol, leukopenia occurred. Leukopenia, immediately before the ophthalmic event, was 1.92 · 103 /ul, for which the patient was placed on an appropriate granulocyte colony stimulating factor.

The best-corrected visual acuity on the day of the examination was 0.3 in the right and 0.6 in the left eye, respectively. Tonometry was within normal values. During the ophthalmological examination of the anterior segment, the presence of rare mutton-fat endothelial precipitates was observed bilaterally, more pronounced on the right, with cellularity in the anterior chamber 2+, pronounced cellularity, especially on the right, was also observed in the anterior vitreous, accompanied by a haze of 2+ on the right , 1+ left. During the funduscopic examination of the right eye, wide pre-equatorial oval ischemic yellow-white areas were observed that extended to the far periphery, confluent in places, and with rare dot hemorrhages. Such retinal ischemic zones were present throughout the entire retinal circumference. On the left eye, the same such lesion was observed in the lower pre-equatorial sector. Echography, OCT of the posterior segment of the eye and fluorescein angiography were performed to further investigate the condition. Ultrasound indicated disturbed exudation in the vitreous and its ablation, OCT findings of the macula and nerve were without pathological changes, while FFA showed hypo to aperfusion zones in the peripheral parts of the retina. In addition, serology for HSV, VZV, CMV, and EBV was performed, with a positive result for VZV and HSV. A vitreal sample was taken for PCR analysis, during which VZV genetic material was isolated, which established the diagnosis of bilateral acute retinal necrosis with subsequent panuveitis in a patient with leukopenia caused by varicella zoster virus.

In consultation with an infectious disease specialist and a hematologist, systemic antiviral therapy was started - Acyclovir in a dose of 800 mg, five times a day for 3 months, followed by a systemic corticosteroid - Prednisone in a dose of 60 mg, two days later, with a gradual dose reduction in the next two months. Additionally, topical corticosteroid and cycloplegic topical therapy was applied due to the inflammation in the anterior segment of the eye as well as oral Aspirin due to the occlusive retinal event. The patient is regularly monitored at our clinic, during the last control the visual acuity has improved, and is 0.6 and 0.9 respectively. Barrage of the right eye was performed with laser photocoagulation to prevent possible ablation of the post-necrotic retinal tissue. Gradually the changes resolved, and in their place remained hyperpigmented scars, the vitritis decreased significantly, but some cellularity persisted in the right eye. The finding of the anterior segment has completely disappeared. The number of leukocytes in the blood count returned to normal values.

Figure 1. Fundus photograph of the right and left eye respectively. Vitritis, yellow-white necrotic retinal lesions temporally and below the macula, retinal hemorrhages.



3. DISCUSSION

The disease is manifested by moderate periocular pain, blurring of vision, photophobia and appearance of floaters. One eye can be affected, but in 1/3 of the cases the other eye is also affected sometime in the first few weeks, but it can also be months and years later (Lei et al., 2020). The clinical picture is characterized by retinal vasculitis

followed by vitritis and subsequent retinal necrosis, i.e. panuveitis. Initially, ARN may present as iridocyclitis with some cellularity in the anterior chamber and endothelial precipitates as well as the formation of posterior synechiae, but within a short period of time the overall manifestation of the posterior segment of the eye occurs. Retinitis is recognized through multiple pale-yellow colored lesions that are confluent and are distributed in the peripheral parts of the retina, they can cover the entire circumference in a few days, especially when the condition is not recognized in time and appropriate treatment is not started. Vasculitis mainly affects arterioles with their occlusion, subsequent choroidal vasculitis, which are the main causes of retinal necrosis. The presence of surrounding retinal hemorrhages is also possible. This phase of the disease is known as the acute herpetic phase. In addition, a moderate to severe degree of vitritis is always encountered, with the possibility of membranous changes forming and the risk of vitreoretinal traction (VRT) and retinal ablation in the late so-called. cicatricial phase (Schoenberger et al., 2017). Retinal ablation is one of the most difficult and common complications of the disease, it occurs in over 75% of cases, and even more so in immunocompromised patients. Mainly, as we mentioned, it is due to VRT with subsequent rhegma, due to devitalized and necrotic retinal tissue that has lost its trophism, but also due to spontaneously formed retinal ruptures at the transition between damaged and healthy tissue (Anthony et al, 2020). Other possible complications are: involvement of the optic nerve-neuritis characterized by edema, dyschromatopsia and relative afferent pupillary defect, vitreal hemorrhage, formation of epiretinal membrane, etc. (Bonfioli & Eller, 2005).

The diagnosis is made clinically according to the characteristic ocular changes, etiologically it can be confirmed with the help of PCR from a vitreal or aqueous sample. In 1994, The American Uveitis Society described diagnostic criteria for ARN and other necrotizing herpetic retinopathies, with which the doctor can more easily be clinically oriented when diagnosing this condition (Holland, 1994).

OCT, FFA, Ultrawild-field imaging can be applied to show the lesion, its complications and monitor the patient.

Differential diagnostics of this disease include: CMV retinitis - especially in immunocompromised patients, progressive external retinal necrosis (PORN), toxoplasma, syphilis, sarcoidosis, primary intraocular lymphoma, Behçet, ocular ischemic syndrome, etc. Some authors consider that PORN is a more severe variant of ARN in immunocompromised patients, while others, that it is a separate entity, due to the different course, worse visual prognosis and difficult response to therapy (Mayer et al., 2022).

The natural course of the disease lasts from 6-12 weeks depending on the individual immunological characteristics of the patient. With the help of antiviral and corticosteroid therapy, the course of the disease is shortened to 4-6 weeks. Antiviral therapy can be applied intravitreally, intravenously or orally, as well as a combination of these ways (Yeh et al 2014). The treatment should last for several months. The most commonly used drug is Acyclovir in a dose of 800 mg, five times a day - per os, however, for therapeutic purposes, Famcyclovir, Valacyclovir, Gancyclovir and Valgancycovir can also be used (Aizman et al., 2007). Gancyclovir and Foscarnet can be applied intravitreally. According to some authors, the use of systemic corticosteroid therapy is controversial and must not be given alone without antiviral therapy. It should be started 24-48 after starting antiviral therapy. The drug of choice is Prednisone in a dose of up to 2mg/Kg/day-per os, for a duration of 6-8 weeks. Aspirin can help prevent further thrombosis of the retinal blood vessels. Local topical corticosteroid and cycloplegic therapy comes into consideration in involvement of the anterior segment of the eye, while local topical antiviral therapy has no effect on the condition (Kawaguchi et al., 2008).

Patients with this condition should be monitored frequently and regularly, in order to promptly detect a possible retinal rhegma, due to the high risk of retinal ablation. Prophylactic laser photocoagulation behind necrotic areas can prevent the occurrence of ablation, but not in all cases, so there is still no consensus on whether or not it should be done in every patient. Timely initiation of antiviral therapy prevents the formation of large retinal lesions, and reduces the risk of involvement of the other eye. In patients with retinal detachment PPV or scleral buckling is a surgical option to manage this severe complication (Dave et al., 2019). The prognosis for visual acuity is different, depending on the degree of retinal necrosis, the duration of the process before starting treatment, the severity of vitritis, and the occurrence of retinal ablation or ischemic optic neuropathy.

4. CONCLUSION

In this paper, we described a case of a patient with ARN caused by varicella zoster virus who possessed certain risk factors for the occurrence of this condition such as: age, leukopenia, immunocompromise due to recent chemotherapy and immunotherapy for the treatment of follicular non-Hodgkin's lymphoma.

Timely diagnosis and appropriate treatment of patients with this ophthalmic condition, especially when it is presented in immunocompromised patients, is of great importance for preserving visual function and preventing numerous ophthalmic and systemic complications.

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