Herpes Simplex Virus Infection of the Anterior Segment of the Eye and its Clinical Presentation. A Review

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SUMMARY

Herpetic infections frequently cause diagnostic errors, which subsequently lead to mistakes in therapy. They affect all the ocular structures, although in everyday practice we most frequently encounter herpetic infections of the anterior segment of the eye. This review article focuses on infections of the anterior segment of the eye caused by the herpes simplex virus. It explains in further detail the specific pathophysiology and course of herpetic infection, which is closely related to the clinical manifestations of the disease. The various stages of primary and secondary infection are described in detail and documented with photographs from the 2nd Eye Clinic of the Slovak Medical University at F.D. Roosevelt Hospital in Banská Bystrica. The last two sections focus on the diagnosis and treatment of herpes simplex virus infections. Correct identification of the form of herpetic disease is crucial for proper therapeutic management.

Key words: herpetic keratitis, HSV 1, HSV 2, dendritic keratitis, disciform keratitis, endotheliitis, antivirotic drugs

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INTRODUCTION

The Herpes Simplex virus is a member of the Herpesviridae family. This is a family of DNA viruses which are the frequent causative agent of infection in humans. Their name is derived from the Greek word herpein (Ἕρπειν), meaning to creep, which reflects the clinical picture of the pathology. As of the year 2020 a total of 115 different herpes viruses had been identified, nine of which cause infection in humans [1]. The most common causative agents are the Herpes simplex virus (HSV), Varicella zoster virus (VZV), Cytomegalovirus (CMV) and the Epstein-Barr virus (EBV). A common trait shared by all members of the Herpesviridae family is the structure of the virion and the complex reproductive cycle, which enables them to transition between a state of active replication and a state of latency [2]. This biological mechanism enables herpes viruses to survive for a long period of time within the host organism and cause recurrent infections [3]. The clinical picture of the pathology is determined by the tropism of the virus to the target cells of the host, the place of latency of the virus and its genetic variability [4].

PATHOPHYSIOLOGY OF THE DISEASE

Based on virus-specific antigens we distinguish between HSV-1 and HSV-2. The majority of ocular complications occur upon a background of HSV-1, with the exception of herpetic keratitis in newborn infants, in which HSV-2 predominates [5]. Primary infection occurs in early childhood, in which the course is mostly asymptomatic or with mild symptoms similar to influenza, with subsequent transition to the latent state [6]. The target of the HSV during primary infection is the nuclei of the ganglion cells, including the trigeminal, cervical, sympathetic and probably also the brain stem. It is here that replication of the virus takes place, in which the cellular immune response does not suppress replication and the virus DNA becomes a part of the DNA of the host cell, where it is hidden from the immune system of the host. Under certain conditions, reactivation of the infection occurs in part of the infected neurons. It is assumed that only 1/3 of the population is exposed to the risk of recurrence, in which the main role is played by the competence of the immune system and stress [4]. A crucial role in the immune system is played by the CD8+ T lymphocytes, which inhibit reactivation of the HSV [7]. On one

hand the immune response is crucial for the elimination of virions and the prevention of direct toxicity associated with infection. On the other hand, negative consequences of the immune response lead to local destruction of tissue and scarring thereof. If the infection is limited to the corneal epithelial layer, a swift immune response is welcome. The faster the infected cells are destroyed, the sooner they are replaced with new ones. In deep forms of herpetic keratitis, immune-mediated inflammation with a cellular component predominates. In this case a vicious cycle ensues, in which the destroyed and broken down cells release the virus into the surrounding area, with the results that the virus then attracts inflammatory cells [8]. All of this leads to serious functional and structural changes to the corneal tissue. These processes are clinically manifested as necrotizing stromal keratitis and immune stromal keratitis. In the case of endotheliitis caused by infection by the HSV virus, delayed hypersensitive reaction to viral antigens predominates [9]. One of the accompanying signs of herpetic keratitis is diminished to extinguished corneal sensitivity. The precise pathophysiology of neurotrophic damage remains contentious, but a role is probably played by damage to the ganglion neurons [4].

CLINICAL MANIFESTATIONS OF PRIMARY INFECTION AND RECURRENT INFECTION

Most primary ocular HSV infections are not identified and have an asymptomatic course or appear as mild uncomplicated conjunctivitis. Approximately 60% of the population is infected with the HSV by the age of five years. Clinical symptoms of primary infection develop in only 6% of those infected, and differ from the symptoms of recurrent infection, which is due to the different response of the immune system. Affliction of the cornea is present in 60% of cases, and the course of keratitis is atypical due to the lack of a formed immune response. Affliction of the deeper layers of the cornea and the presence of iridocyclitis is not typical of primary HSV infection [10]. Recurrent HSV infection is manifested in affliction of a variety of ocular structures, and causes clinical conditions of varying incidence and varying clinical severity. A clinical manifestation of affliction of the skin of the eyelids is herpetic blepharitis, which often does not require local antivirotic therapy, although this is often prescribed [11]. In terms of diagnosis and therapeutic approach, keratitis is the most serious complication of ocular pathology caused by the HSV virus. Types of HSV keratitis are presented in Table 1 according to the affected structures of the cornea, as published by Holland and Schwarz in 1999 [12]. Dendritic or geographic ulcers are the most common manifestations of viral damage to the epithelium, generated by damage to the epithelial cells by the multiplying virus (Figure 1). After healing of the epithelial defect, dendritic epitheliopathy may persist. It is important to differentiate this stage of healing from active infection, because it may create a false impression of an insufficient response to antiviral therapy [10]. When the spreading of the epithelial defect and loss of its linearity and branching occurs, this is referred to as a geographic ulcer. It is frequently caused by iatrogenic local administration of corticosteroids (Figure 2). Another form of epithelial damage caused by HSV infection is marginal keratitis. The anatomical relationship to the limbus and blood vessels is the reason for this specific clinical manifestation, which incorporates infiltration of the anterior stroma through the cells of the immune system and pronounced perilimbal hyperemia [10]. A serious complication of epithelial herpetic keratitis is the onset of neurotrophic keratopathy. This condition is known as a metaherpetic corneal ulcer. Its development is not caused by direct activity of the virus or by the excessive immune response of the host, but rather by a disorder in the healing process of the corneal tissue. Of crucial significance here is the impairment of the innervation of the cornea, followed by a reduction of the quantity and quality of tears. Damage to the sensory innervation of the cornea leads to changes on the level of the neuromodulators, which are of crucial importance for the vitality and metabolism of the epithelial cells. In addition

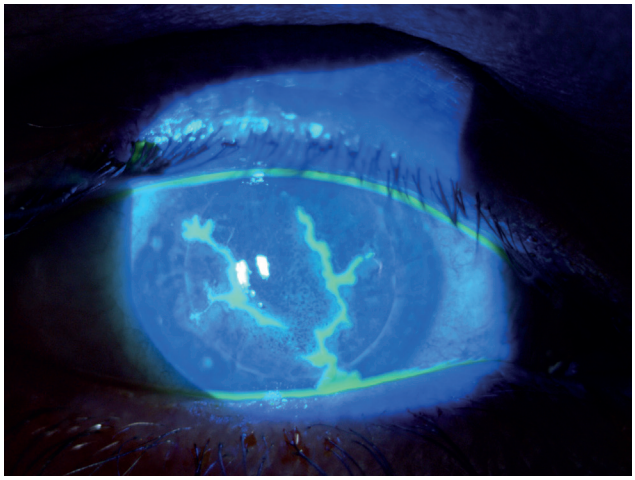

Figure 1. Dendritic keratitis of the graft in a patient after penetrating keratoplasty

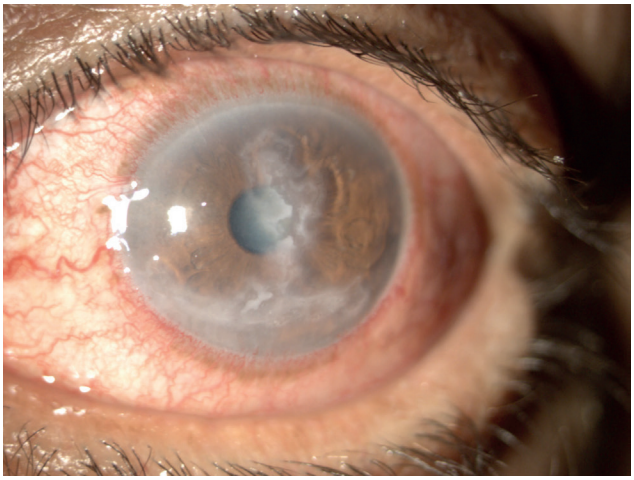

Figure 2. Geographic herpetic corneal ulcer in a patient treated with topical corticosteroids

Table 1. Classification of HSV keratitis according to Holland and Schwartz [12]

Corneal layer	Clinical manifestation
I. Infectious epithelial keratitis	corneal vesicles
	dendritic ulcer
	geographic ulcer
	marginal ulcer
II. Neurotrophic keratopathy	epithelial erosions corneal surface defect
III. Stromal Keratitis	Necrotizing stromal keratitis
	Immune stromal (interstitial) keratitis
IV. Endothelitis	disciform
	diffuse
	linear

HSV – Herpes virus simplex

to the above-mentioned, regeneration of the epithelium is reduced also by the toxic effects of anti-infective therapy. All of this occurs upon a background of persistent epithelial defect with chronically ongoing inflammation [10]. Another clinically significant and common form of corneal affliction by the HSV is affliction of the corneal stroma. The term "stromal keratitis" in HSV infection is often erroneously used for different conditions. Such generalization may subsequently lead to the application of inappropriate therapy. Affliction of the stroma may be either primary or secondary. Primary stromal affliction with HSV infection is represented by two clinical units, namely necrotizing stromal keratitis and immune-mediated stromal keratitis [9]. Necrotizing keratitis is a rarer form of corneal infection with the HSV, with an adverse prognosis. Direct stromal infiltration by the virus and its intracellular multiplication in keratocytes dominates in the etiology, which leads to destructive inflammation that is often resistant to treatment [10]. Another form of direct stromal damage caused by the HSV is immune-mediated stromal keratitis. This is a common form of recurrent HSV infection. An immune response mediated by T-lymphocytes to the viral antigen complex in the corneal tissue and complement predominates in the etiopathogenesis [13]. It may occur a few days or even several years after the preceding episode of epithelial herpetic keratitis, which leaves viral antigens in the corneal stroma. The clinical course is chronic and recurring, and may persist for years. Complete remission of the disease with subsequent repeated severe recurrence in patients is not a rare occurrence. A frequent accompanying sign of immune-mediated stromal keratitis is neovascularization of the stroma of varying intensity, from a few small vessels to circular infiltration of the cornea (Figure 3A, B). Neovascularization may complicate the accumulation of lipids, which leads to a reduction of corneal transparency. Following suppression of immune-mediated information and neovascularization, small vascular channels remain left by the capillaries in the corneal tissue. In most cases they do not lead to a deterioration of visual acuity, but they play a role in recurrences of the disease. A specific secondary affliction of the stroma is endotheliitis, which is a synonym for disciform keratitis. In the literature and in clinical practice, the term disciform keratitis is often erroneously used in the case of inflammatory affliction of the corneal stroma. The difference between these clinical units is evident. The term "endotheliitis" describes sterile immune inflammation aimed at the HSV antigens in the cells of the corneal endothelium. Unlike stromal keratitis this concerns an inflammatory reaction on the level of the endothelium, with secondary affliction of the stroma as a consequence of endothelial dysfunction (Figure 4). Neither cellular infiltration or neovascularization is present in the stroma. Similarly as in the case of immune-mediated stromal keratitis, an episode of disciform keratitis may occur months to years after the patient has overcome infectious epithelial keratitis [14]. Herpetic infection of the anterior segment of the eye is often accompanied by iridocyclitis and an increase in intraocular pressure, though the elevation of intraocular pressure is not generally pronounced. The difference in comparison with

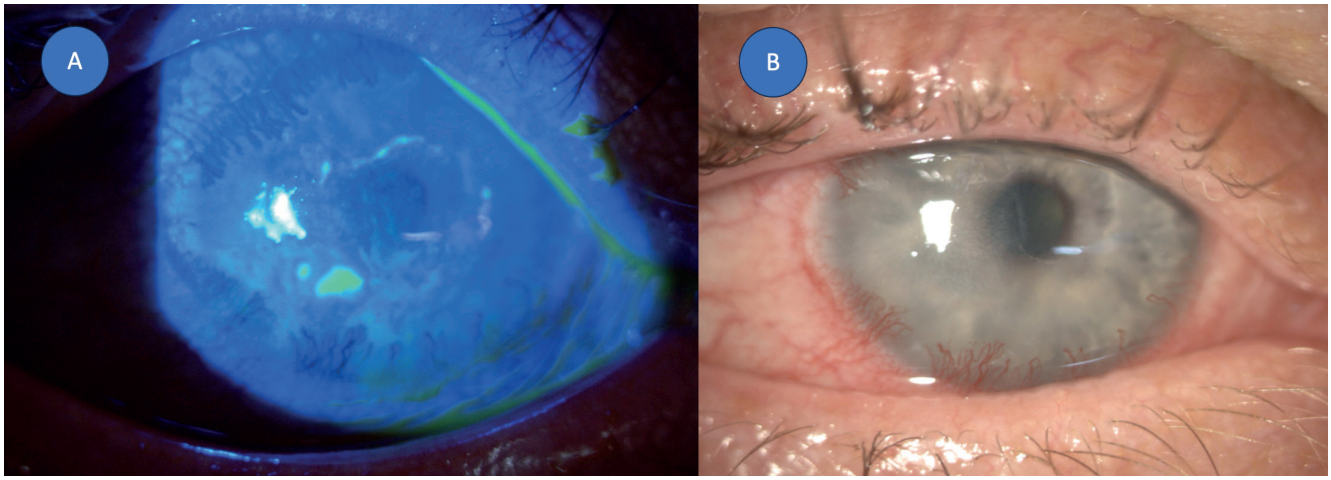

Figure 3. Stromal immune keratitis with corneal neovascularization and epithelial defect – (**A**) image with fluorescein dye, (**B**) image without fluorescein dye

the unaffected eye may be only 5 mmHg. If a pronounced increase of intraocular pressure predominates in the clinical picture without a manifest inflammatory reaction in the anterior part of the eye, trabeculitis is suspected [11].

DIAGNOSIS

In clinical practice, diagnosis of herpetic infection is determined on the basis of the clinical presentations. In the case of diagnostic uncertainty or severe states (and in all cases of neonatal herpetic infections) it is possible to use objective laboratory examination methods, which can be divided into four groups: 1) cultivation examination, 2) microscopic examination of biological material (skin, conjunctival and corneal swabs), 3) molecular and immunological tests, and 4) determination of antibodies. Cultivation of the virus incorporates isolation of the virus from the bodily fluids or tissues and its subsequent cultivation in laboratory cell lines. This method provides direct evidence of the presence of the virus in the examined sample of tissue, it has 100% specificity and is used as a referential method for comparing the effectiveness of other tests. The main disadvantages are the time demand factor (minimum 10 days) and lower sensitivity [15]. Another group of laboratory diagnostic methods is represented by cytopathological examinations. The sample is thermally fixed, applied to a glass slide and stained before the microscopic examination. The simplest and most basic staining is the method according to Giemsa or Wright. Tissue afflicted by herpetic infection is typified in the microscopic image by a finding of multinucleated cells with balloon degeneration and infiltration of mononuclear and polymorphonuclear leukocytes. Although these techniques are quicker in comparison with cultivation techniques, the result is less specific. A significant advance in diagnosis has been brought by the PCR (polymerase chain reaction) method [16]. This is a highly sensitive and specific method for direct detection of virus DNA. The advantage of PCR is its high sensitivity, which enables detection even of a very small quantity of the virus. PCR is commonly used for the detection of the virus in the lacrimal film and in the corneas of patients. This examination is also specific, but more sensitive than an examination with the use of cell culture, and thanks to the quick diagnosis it is currently the preferred diagnostic method. The condition is the stage or character of the herpetic pathology provided by the virus particles, which is for example epithelial herpetic keratitis, herpetic conjunctivitis or skin affliction. It is not applicable in the case of stromal or endothelial keratitis [16]. The last group of diagnostic options is serological determination of antibodies. There are a number of different laboratory methods for determining antibodies, although the most widely used is the ELISA method (enzyme-linked immunosorbent assay). The method uses antigen-antibody binding, in which an enzyme catalyzing a chemical reaction is bound to one of these components, with the resulting product being spectrophotometrically or fluorescently readable. The ELISA method can be used for direct detection of the viral antigen in the blood, or more commonly for determining antibody titer of the ongoing immune response. Class IgM antibodies are present in serum during primary and sometimes also during recurrent infection, in which an increased concentration thereof persists for several weeks with progressive seroconversion to class IgG [17]. The concentration of IgG antibodies increases after one to two weeks, but persists for a substantially longer period. A number of authors have investigated the option of differentiating between primary and recurrent infection on the basis of the concentration of IgM and IgG antibodies. Based on an observation of cohorts of patients they came to the conclusion that the concentration of class IgG antibodies does not correspond to the severity of the clinical picture upon recurrent herpetic infection, and mostly remains constant before, during and after an episode of herpetic ocular infection. Only a small percentage of patients in these observed cohorts manifested a corresponding change in the concentration of IgG antibodies in connection with an episode of herpetic keratitis [18].

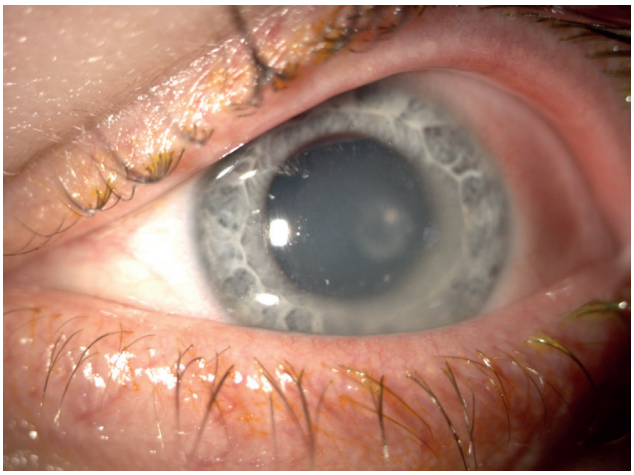

Figure 4. Disciform keratitis caused by herpes simplex virus

TREATMENT

The basic anti-infection treatment is antivirotic drugs. These are analogs of nucleic acids. The essence of their effect is inhibition of viral DNA polymerase, thereby causing a change in the synthesis of viral DNA. The drugs can be divided into two groups – selective and non-selective. Original preparations such as idoxuridine, vidarabine and trifluridine belong to the group of non-selective antivirotic drugs. Their active form is generated by phosphorylation in the cells affected by the virus, as well as those not affected by the virus. This results in undesirable toxicity to the healthy tissue. This observation led to a search for newer, "elective" antivirotic drugs, in which phosphorylation takes place only by means of viral thymidine kinase, thereby reducing the toxicity towards the host cells. Representatives of selective antivirotic drugs are acyclovir, ganciclovir, valaciclovir and famciclovir. Another essential pharmacological group in the treatment of herpetic infection of the anterior segment of the eye is corticosteroids. The aim of

Table 2. Overview of hypotheses and results from the Herpetic Eye Disease Study group of clinical trials [19]

Clinical Study Hypothesis	Clinical Study Outcome
Are topical corticosteroids effective in the treatment of stromal keratitis?	Corticosteroids significantly reduce the level of stromal infiltration and shorten the duration of the disease.
Does oral acyclovir provide benefits in the treatment of stromal keratitis treated with topical corticosteroids and trifluridine?	No benefit of oral acyclovir was observed in cases of immune stromal keratitis.
Does oral acyclovir provide benefits in the treatment of herpetic iridocyclitis?	A statistically insignificant benefit of oral acyclovir was found in patients with iridocyclitis.
Does oral acyclovir provide benefits in preventing the development of stromal herpetic keratitis and iridocyclitis in patients treated for epithelial herpetic keratitis?	No difference in the development between the groups treated with oral acyclovir and placebo was observed.
Does oral prophylactic acyclovir reduce recurrent HSV infection?	50% less frequent recurrence of HSV infection in the group with prophylactic acyclovir compared to placebo.
Triggers for the reactivation of herpetic keratitis.	No clear identification of triggers.

Table 3. Overview of possible surgical approaches in herpetic infection of the anterior segment of the eye [11]

Anterior Segment Involvement	Surgical Procedure
Neurotrophic keratopathy and deep corneal ulcer without immediate perforation	Amniotic membrane Elective perforating keratoplasty
Neurotrophic keratopathy and deep corneal ulcer with impending perforation	Amniotic membrane Tissue adhesive Perforating keratoplasty and chaud
Corneal scars (depending on the depth of the scar)	Perforating keratoplasty DALK Phototherapeutic keratectomy
Bullous keratopathy as a result of endothelitis	Perforating keratoplasty DALK DMEK DSEK
Secondary glaucoma	Cyclodestructive glaucoma surgeries Filtration glaucoma surgeries
Cataract	Phacoemulsification and IOL implantation

DALK – deep anterior lamellar keratoplasty, DMEK – descemet membrane endothelial keratoplasty, DSEK – descemet stripping endothelial keratoplasty, IOL – intraocular lens

applying corticosteroids is to suppress the immune mechanisms to the extent that the antiviral potential is retained, but any further excessive immune response is suppressed. Their use is of crucial value in immune-mediated forms of herpetic keratitis. Examples are forms of herpetic stromal keratitis, endotheliitis and iridocyclitis. By contrast, their application is strictly contraindicated in the case of epithelial keratitis, in which active multiplication of the virus is present. Corticosteroid treatment is applied always in combination with full local or systemic antivirotic treatment [6]. In the case of stromal keratitis and endotheliitis with frequent recurrence, long-term local administration of corticosteroids is no exception. The rule of "as little as possible" "for as long as necessary" applies. Reduction should be gradual, never by more than 50% of the current dose. The higher the "peak" dose, the more rapidly it is possible to reduce treatment, whereas by contrast the lower the dose, the more gradual the reduction of treatment should be. Some patients may also profit from dosage every other day or even once per week in preventing reactivation of stromal pathology [11]. Questions relating to the practical problems of medicamentous therapy of herpetic infection of the anterior segment of the eye were investigated in a number of multicentric, randomized, placebo-controlled clinical trials affiliated under the title of the Herpetic Eye Disease Study in 1994. An overview of the hypotheses and results of the group of clinical trials is presented in Table 2. In the case of damage to the epithelial layer, as well as in the case of epithelial dendritic or geographic herpetic keratitis, intensive lubrication therapy is appropriate, as well as local prophylactic antibiotic treatment. Cycloplegic drugs are also appropriate in the case of inflammatory reaction in the anterior chamber, or if the patient suffers pronounced pain and photophobia. A separate chapter concerns anti-glaucomatous drugs in the case of decompensation of intraocular pressure or trabeculitis. Some authors use "debridement" of the affected epithelium in the case of a dendritic or geographic ulcer upon a background of

epithelial keratitis. However, the benefit of this approach is questionable. In the case of exhaustion of medicamentous therapy and the persistence of an epithelial defect or danger of corneal perforation, it is necessary to proceed to surgical intervention. They are therefore applicable mainly in the case of neurotrophic keratopathy, extensive epithelial geographic corneal ulcers and in extreme cases of necrotizing interstitial keratitis. There are a number of surgical procedures, which differ in their indication, scope and last but not least the demand factor of their performance. An overview is presented in Table 3.

CASE REPORT

The case report focuses on a 27-year-old male patient with herpetic endotheliitis and keratouveitis in his left eye. His complaints ensued after suffering a chemical burn in an industrial accident (7/2023). He sought attention from an ophthalmologist on 8 August 2023. According to the available documentation his condition was concluded as deep keratitis, with subsequent hospitalization. During hospitalization a cultivation examination confirmed the presence of Streptococcus viridans and Staphylococcus epidermidis, and local antibiotic treatment was subsequently applied (levofloxacin, propamidine isethionate), as well as general antibiotic treatment (cefixime), local and general antimycotic treatment (fluconazole), local corticosteroid treatment (loteprednol), general corticosteroid treatment (prednisolone) and cycloplegic treatment. Despite the administered therapy the patient's condition deteriorated, and as a result he was referred to the 2nd Eye Clinic of the Slovak Medical University. The first examination at our center was conducted on 20 September 2023. Initial best corrected visual acuity in the right eye was 1.0, in the left eye fingers in front of the eye. At the baseline examination on the left eye, in the local finding there was predominant reduced transparency and corneal edema with disciform infiltrate in the deep stroma. The inflammatory reaction in the anterior chamber was not pronounced, although organized precipitates were present on the endothelium (Figure 5). We proceeded to adjust the local antibiotic treatment (gentamicin, chloramphenicol/dexamethasone) and general antimycotic treatment (voriconazole). We left the remaining treatment unchanged. The patient's condition did not improve even after we adjusted the therapy. As part of the investigation into the possible etiology of the disease, a PCR sample from the cornea and a cultivation tests were added, but did not demonstrate the presence of a pathogen. A serological examination demonstrated increased class IgG antibodies to HSV, CMV, VZV and borderline class IgM antibodies to EBV. On this basis the patient's diagnosis was reclassified as herpetic endotheliitis with subsequent reduction and adjustment of local antibiotic treatment and corticosteroid treatment to one mixed preparation (fluoroquinolone/dexamethasone and tobramycin/dexamethasone). The local antiglaucomatous drug carteolol was added due to an increase of intraocular pressure. With regard to the general therapy, the antibiotic and antimycotic treatment were progressively reduced, and full antivirotic treatment was added (acyclovir). This adjustment of the treatment was followed by a subjective and objective improvement of the patient's condition. Corneal transparency improved, with progressive subsidence of corneal stromal edema. Disciform infiltrate remained present in the deep stroma and on the endothelium (Figure 6). The patients was discharged on 4.10.2023 with corrected visual acuity in the right eye of 1.0 and in the left eye of 0.63. The patient's condition improved further at follow-up examinations in outpatient care, and at his last visit on 26.2.2024 the patient's best corrected visual acuity in the right eye was 1.0 and in the left eye also 1.0. Opacification and corneal edema were completely eliminated, only se-

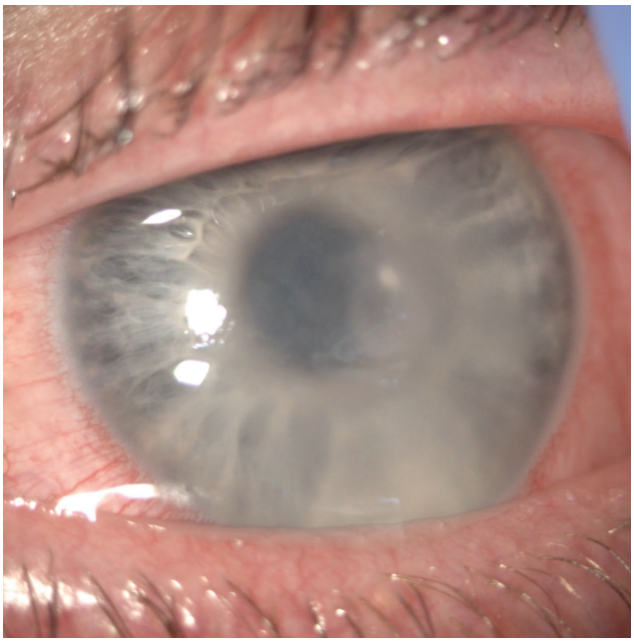

Figure 5. Baseline image of the anterior segment of the left eye in the case report patient. Reduced transparency and corneal edema with disciform infiltrate in the deep stroma are present

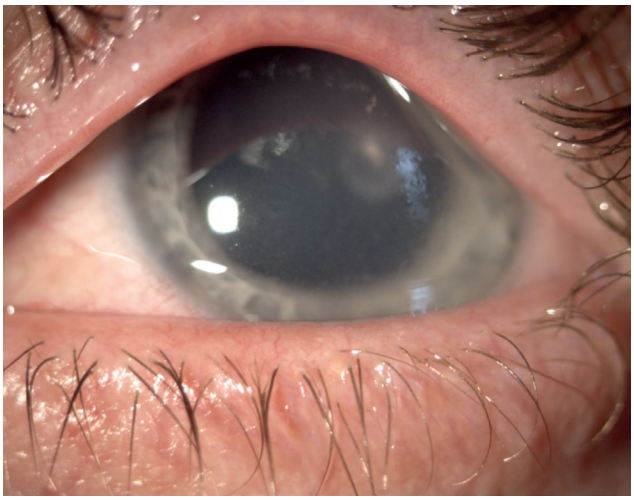

Figure 6. Image of the anterior segment of the left eye in the case report patient after initiation of antiviral treatment

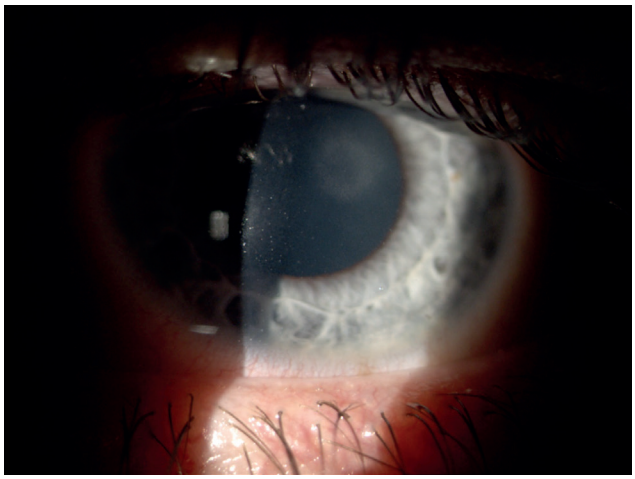

Figure 7. Image of the anterior segment of the left eye in the case report patient at hospital discharge. Reduced transparency and corneal edema are improved; semipigmented deposits are present on the endothelium

mi-pigmented deposits remained on the endothelium (Figure 7). The patient is continuing in maintenance antivirotic treatment (acyclovir) and local corticosteroid treatment (fluorometholone). The presented case emphasizes the importance of accurate diagnosis and corresponding treatment of the patient. The initially selected local and general antibiotic and antimycotic therapy did not bring about the desired improvement of the patient's condition. It was not until an extended serological test was conducted that the possibility of herpetic etiology was indicated. Disciform keratitis is a manifestation of recurrent herpetic infection (in this case probably EBV), where the dominant role is played by the immune response of the organism. As a result, the patient's condition improved dramatically after the administration of a combination of corticosteroid and antivirotic therapy. A correct diagnostic approach from the beginning could have saved the patient a considerable amount of time spent in hospital facilities.

CONCLUSION

Herpetic infections of the eye represent a significant and common medical problem because of their potentially serious complications and influence on the patient's visual functions. The herpes simplex virus (HSV) plays a key role in the etiology of these pathologies, in which its capacity to persist in latent form and reactivate under certain conditions significantly complicates the management of infection. No less important is the mechanism of damage to the corneal tissue, which differs markedly upon affliction of the corneal epithelium when the virus actively multiplies within the cells, and the therapeutic choice is antivirotic drugs. A different case is represented by stromal and endothelial keratitis, in which a key role is played by the organism's immune system, and the therapeutic choice is corticosteroids. The situation is also complicated by the fact that corticosteroid treatment significantly worsens epithelial herpetic keratitis if it suppresses the mechanisms of the immune system, while on the other hand immune-mediated stromal and endothelial keratitis cannot be cured only by the administration of antivirotic therapy. Mistaking the forms of herpetic keratitis and inappropriate treatment may therefore have serious consequences for the patient. For this reason, accurate and timely diagnosis, based predominantly upon clinical manifestations and supported by laboratory methods, is essential for successful treatment.

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