CYTOMEGALOVIRUS ANTERIOR UVEITIS

Kotingová Veronika, Fichtl Marek, Brichová Michaela, Svozílková Petra, Klímová Aneta, Rezková Lucie, Škrlová Eva, Heissigerová Jarmila

Department of Ophthalmology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic

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MUDr. Veronika Kotingová
Oční klinika, 1. LF UK a VFN v Praze
U Nemocnice 499/2
12808 Praha 2
E-mail: veronika.kotingova@vfn.cz

SUMMARY

Aim: The aim of the article is to summarize observations on cytomegalovirus (CMV) anterior uveitis, and in short case reports present cases of patients treated at our Department of Ophthalmology, First Faculty of Medicine, Charles University and General University Hospital in Prague.
Material and methods: Retrospective analysis of patients at the Centre for diagnosis and treatment of uveitis from 2003 to 2024. Presentation of our experiences with CMV anterior uveitis confirmed by polymerase chain reaction (PCR) in aqueous humor in case reports.
Results: From a cohort of 3844 patients with uveitis, 3 patients were diagnosed with CMV anterior uveitis, confirmed by PCR in the aqueous humor. The clinical presentation was as acute recurrent hypertensive anterior uveitis in all patients, with a switch to chronic form with elevated intraocular pressure (IOP). Despite local anti-inflammatory and antiglaucomatous therapy, there was high recurrence of uveitis with decompensation of IOP when the medication was reduced. Patients underwent antiglaucoma surgery because of persistent high IOP despite maximal local antiglaucomatous therapy. An anterior chamber tap was taken for PCR analysis, with a CMV-positive result. After the initiation of antiviral therapy with local ganciclovir, patients manifested compensated IOP and a pronounced reduction of recurrences of uveitis and progression of glaucoma.
Conclusions: CMV anterior uveitis is a rare pathology in our geographic region, but it is important to consider this etiology in cases of recurrent anterior hypertensive uveitis with a low response to local anti-inflammatory medication. Timely verification of the etiological agent with prompt diagnosis and treatment is essential in order to achieve a favorable prognosis. Long-term, low maintenance doses of antiviral therapy with local ganciclovir for several months reduce relapses of uveitis and lead to compensation of IOP.
Key words: cytomegalovirus, anterior uveitis, secondary glaucoma, ganciclovir

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INTRODUCTION

Cytomegalovirus is a DNA virus belonging to the class of herpesviruses. The level of antibodies within the population is high, but due to its low virulence it is clinically manifested only minimally. In the latent phase the virus survives in the myeloid progenitor cells, and has been identified in the eye within the smooth muscle tissue of the iris, ciliary body, the trabecular meshwork and the corneal endothelium [1]. It may be reactivated upon a decrease of immunity or upon application of immunosuppressant preparations, and following ocular surgical procedures [1–3]. In immune compromised patients CMV may affect the retina as CMV retinitis. In immune competent patients ocular afflictions are most frequently manifested as acute anterior uveitis [4–6]. The highest incidence of the pathology is in Asiatic males, and it is rare within our geographical region [6,7]. Clinically it may be manifested as acute recurrent hypertensive anterior uveitis within the framework of Posner-Schlossman syndrome (PSS), chronic anterior uveitis analogously as Fuchs uveitis syndrome (FUS) or as CMV entotheliitis [1–3,8].

Acute recurrent anterior uveitis predominantly affects men aged between 30 and 50 years, and is clinically manifested as PSS, in which CMV is one of the causes. In most cases it takes place as mild unilateral anterior uveitis without pronounced ciliary injection, with a high elevation of IOP up to 50 mmHg and corneal edema. Whitish or grey small to medium-sized precipitates are present in the center or on the periphery of the endothelium, more in the lower half, frequently accompanied by endotheliitis [1–3,6,9]. In rare cases the formation of stromal lesions of the cornea has been observed [1]. In the anterior chamber there is a minimal finding of cells and flare [8,10]. Atrophy and depigmentation of the iris may be present [11,12]. The pupil is generally rounded, in rare cases slightly dilated [1].

Chronic anterior uveitis is also unilateral in most cases, and appears mainly in men aged over 50 years. In Asia-

tic individuals it is clinically manifested as typical FUS, in which CMV is one of the most common causes [1–3]. In patients in Western European and North American countries there is greater variability of the clinical picture, specifically mild anterior uveitis with chronic elevation of IOP, lower quantity of pigmented precipitates in the lower half of the endothelium, and frequent presence of endotheliitis. Diffuse ("moth-eaten") and less commonly sectoral atrophy of the iris may occur, without manifest transillumination, heterochromia is rare [1,3,4,6,7]. There is often a combination of both syndromes, most frequently beginning as PSS with gradual transition to chronicity [1,2]. Posterior synechiae do not typically occur in either form [1–3,9,13]. Gonioscopically an open chamber angle is evident, in rare cases anterior synechiae and more pronounced pigmentation of the angle [3,9]. Subjectively it is manifested in blurred vision, sensitivity or mild pain of the eyeball to hemicrania upon a high elevation of IOP. However, it may have an asymptomatic course, mainly in the case of the chronic form [4,5,9,10].

CMV endotheliitis is an inflammatory affliction of the endothelium with presence of typical nummular lesions of the endothelium (or coin-shape opacities), with circularly structured fine precipitates, less frequently linear lesions with precipitates localized in the corneal periphery, and with local edema. In the anterior chamber there is generally mild inflammatory activity, which may be accompanied by elevation of IOP [14,15]. Endotheliitis may lead to a gradual reduction of the number of endothelial cells and the degree of loss significantly correlates with the viral load in the aqueous humor [16,17].

In differential diagnosis we consider other herpesviruses, mainly the herpes simplex virus (HSV) and the varicella-zoster virus (VZV). Their differentiation is not a simple matter, and the differences between the individual viruses and their clinical manifestation is illustrated in Table 1 [2,3]. The main features attesting to CMV etiology are mild anterior uveitis and the absence of posterior synechiae [1,4,5]. The presence of typical coin-shaped lesions on the endothelium is a pathognomonic finding attesting to this etiology in 90% of cases [4–6,13,14]. Precise diagnosis depends upon PCR verification of the virus in the aqueous humor. Serology of viruses is not a conclusive examination due to the high prevalence of anamnestic antibodies against CMV within the population, and the result may not reflect the ocular pathology [5]. Therapy consists in the administration of antiviral therapy, specifically ganciclovir locally (drops, gel, intravitreally) or valganciclovir systemically (orally) [2–4,9]. Another essential therapy is locally administered corticosteroids (prednisolone or dexamethasone), which suppress the inflammatory reaction, and antiglaucoma therapy upon elevation of IOP. Frequent complications are secondary glaucoma and complicated cataract [1,6,8]. In rare cases corneal decompensation may occur, with the necessity for transplantation [5,14]. In the case of decompensation of IOP despite maximum antiglaucoma

Table 1. Comparison of clinical features between herpetic viral anterior uveitis etiologies

VIRUS	HSV	VZV	CMV
AGE (YEARS)	< 50	> 60	acute > 30, chronic > 50
SEX	no predilection	no predilection	male predilection
RACE	all	all	typical Asian
SYMPTOMS	severe	severe	mild or absent
INTRAOCULAR PRESSURE	acute spikes	acute spikes	very high, up to 50 mmHg
KERATIC PRECIPITATES			
DISTRIBUTION	Arlt´s triangle, inferior part	Arlt´s triangle, inferior part	centrally, peripherally or diffuse
MORPHOLOGY	medium to large	medium to large	small to medium, coin-shaped
COLOR	white to pigmented	white, in chronic pigmented	white to gray, in chronic pigmented
DERMAL MANIFESTATION	vesicular rash	dermatomal rash	none
CORNEAL	dendritic ulcers	pseudodendritis ulcers	rare stromal lesion
IRIS ATROPHY	sectoral	sectoral, spiral	stromal atrophy (moth eaten)
PUPIL	eccentric dilated to plegic	eccentric dilated to plegic	round, not posterior synechiae
SENSATION OF CORNEA	could by lower	could by lower	not affected
LATERALITY	typically unilateral	typically unilateral	mainly unilateral, rare bilateral
ENDOTHELIITIS	less frequent	less frequent	more frequent, typical coin shaped lesion

HSV – herpes simplex virus, VZV – varicella-zoster virus, CMC – cytomegalovirus

therapy, timely performance of an antiglaucoma surgical procedure is indicated. Long-term local or general oral therapy with ganciclovir/valganciclovir in low doses is recommended in order to reduce the risk of relapses of inflammation, which involve loss of endothelial cells and progression of glaucoma [4,5,17,18].

MATERIAL AND METHODS

A retrospective analysis was conducted on a cohort of patients from the Center for Diagnosis and Treatment of Uveitis at the Department of Ophthalmology, 1st Faculty of Medicine, Charles University and General University Hospital in Prague from 2003 to 2024. The study focuses on a presentation of our own experiences with PCR-verified patients with CMV anterior uveitis in the form of case reports. In our cohort of patients, we measured best corrected visual acuity (VA) in both eyes, IOP by noncontact tonometry, we performed gonioscopy using a Goldmann lens, examined the anterior segment and biomicroscopically examined the posterior segment of the eye. Using special examination methods we performed glaucoma perimetry, optical coherence tomography in order to assess the thickness of the nerve fibers (OCT of RNFL), and confirmation of the etiological agent with the aid of PCR from the aqueous humor.

RESULTS

Out of a total of 3844 patients monitored with uveitis (100%), of whom 343 patients had anterior herpetic uveitis (8.9 %), 12 patients were recorded with suspected CMV anterior uveitis (0.3%), out of whom 3 patients (0.08%) were confirmed with this condition by means of PCR analysis. We present their case reports below.

Patient no. 1, a man aged 52 years, was referred to our center due to suspected PSS in the right eye (RE), with elevation of IOP. From his ocular medical history, he described a similar attack in the past. His general condition was healthy, without long-term ocular or general medication. The therapy applied was a combined preparation of dorzolamide and timolol 2x per day and dexamethasone 5x per day. VA in both eyes was 1.0 naturally. IOP in RE was 28 mmHg, small whitish precipitates were present on the endothelium, in the anterior chamber minimally cells, the iris was thinned nasally with dilated blood vessels. Reduction of local anti-inflammatory therapy led to a reactivation of anterior uveitis with an elevation of IOP to 40 mmHg. The response to dexamethasone was progressively weaker, rounded plaques appeared clinically with precipitates on the endothelium, diffuse dilation of blood vessels and hemorrhage of the iris, the pupil was dilated (Figure 1). Peripheral anterior synechiae were perceptible in places gonioscopically. Due to suspicion of herpetic etiology, oral therapy with acyclovir was administered in an overall dose of 2 g per day, with ganciclovir 0.15% gel locally 3x per day. Due to persistent decompensated IOP even with maximum antiglaucoma therapy, trabeculectomy was performed with an Ologen® implant, and a sample of the aqueous humor was taken for PCR analysis of herpesviruses. The sample demonstrated positivity of CMV, while HSV and VZV was negative. Postoperatively compensation of IOP took place, on the anterior segment pigmented precipitates were present in the lower half of the cornea without signs of endotheliitis, iris with coloboma by no. 10 and lens with incipient opacity (Figure 2). After that surgery of complicated cataract was performed with postoperative VA 1,0. Reactivation of anterior uveitis with endotheliitis was found while doses of ganciclovir was detracted, in one case subepithelial lessions appeared (Figure 3). Atrophy of the stroma of the iris took place progressively. Precipitates appeared repeatedly also on the endothelium of the left eye (LE), with occasional elevation of IOP, after administration of local therapy with ganciclovir 0.15% gel combined with dexamethasone we recorded a progressive regression of the symptoms. OCT of RNFL and glaucoma perimetry were within the limits of the norm throughout the entire observation period. Up to the present time the patient has compensated IOP without therapy, anterior segment without inflammation and a maintenance dose of ganciclovir 0.15% gel locally 1x per day in RE.

Patient no. 2, a woman aged 26 years, was referred to our department due to recurring anterior uveitis in LE with elevation of IOP, not responding to anti-inflamma-

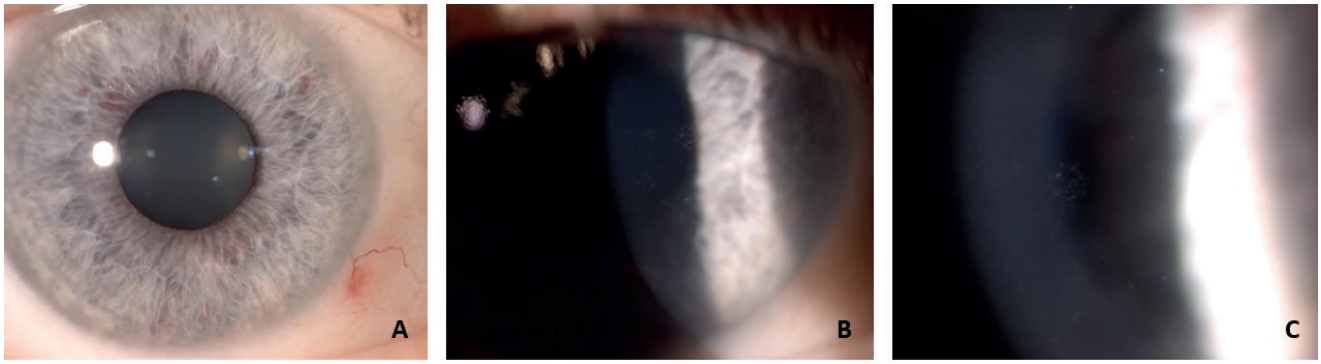

Figure 1. Patient no.1: (**A**) Anterior segment in activity – eye without injection, keratic precipitates and endotheliitis on the cornea, iris with hemorrhage and dilated vessels, lightly dilated pupil. (**B**) Endotheliitis – coin-shaped keratic precipitates on endothelium. (**C**) Coin-shaped lesion in detail

tory therapy and newly with dilation of the pupil in the affected eye. The patient suffered her first attack at the age of 16 and in the recent period has been experiencing recurrences at minimum once per year, always in the same eye. The patient's general condition was healthy, without long-term local or general medication. Due to the presence of anisocoria she was referred urgently for a neurological examination, without determination of pathology. VA in both eyes was 1.0 with correction. Deposits of endotheliitis were present on the anterior segment of LE, anterior chamber with cells 1+ and minimal flare, pupil rounded, dilated, with retarded reaction (Figure 4), normotension in both eyes, in left on locally administered combined preparation of dorzolamide and timolol 2x per day and dexamethasone 3x per day. In differential diagnostics PSS, CMV anterior uveitis and herpetic anterior uveitis (HSV) were considered. Ganciclovir 0.15 gel was added locally 5x per day, and dexamethasone was increased to 5x per day. Acyclovir was added, administered generally in a dose of 2 g per day. At further follow-up examinations IOP fluctuated around the level of 30 mmHg and local antiglaucoma therapy was increased to the maximum tolerable therapy. Alleviation of the inflammation progressively occurred, with regression of endotheliitis, almost complete correction of pupil width and compensation of IOP. Upon reduction of local antiviral and anti-inflammatory therapy we again recorded an elevation of IOP up to 35 mmHg, and mild uveitis without signs of endotheliitis, furthermore with pigment dispersion on the endothelium of both eyes. Increased pigmentation was perceptible in LE gonioscopically, without goniosynechiae. Glaucoma perimetry in the patient was

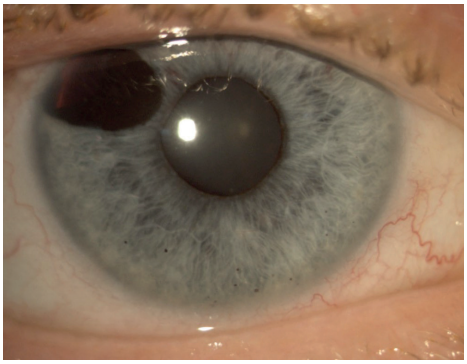

Figure 2. Anterior segment afret trabeculectomy – older pigmented keratic precipitates in lower part of cornea without endotheliitis, basal coloboma, incipient cataract

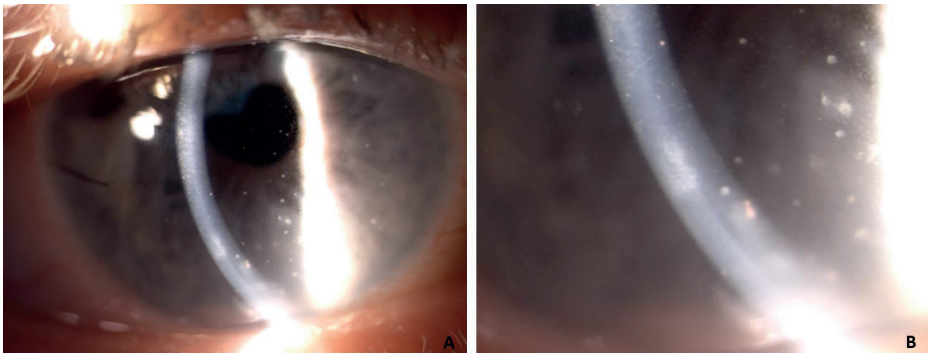

Figure 3. (A) Anterior segment in activity with white and older pigmented precipitates, endotheliitis and subepithelial lesions of cornea localized centrally and peripherally. (**B**) Subepithelial lesion of cornea in detail

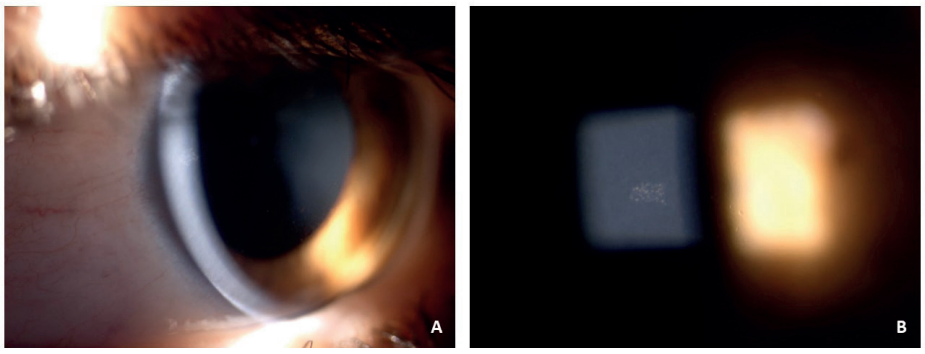

Figure 4. Patient no. 2: (**A**) Anterior segment in activity – eye without injection, small white and pigmented endothelial precipitates and endotheliitis on the cornea, round dilated pupil. (**B**) Coin-shaped keratic precipitates in detail

without any defect in the visual field. Due to persistent decompensation of IOP, trabeculectomy was performed with an Ologen® implant, and a sample of the aqueous humor was taken for PCR analysis of herpesviruses. The result was positive for CMV. Postoperatively the patient was several months with compensated IOP without antiglaucoma therapy, on a maintenance dose of ganciclovir 0.15% gel 2x per day and fluorometholone 2x per day. Exacerbation of uveitis occurred even despite therapy, with presence of whitish precipitates on the endothelium and in one case also subepithelial lesions on the cornea (Figure 5), progressively with decompensation of IOP and the necessity to increase antiglaucoma therapy. At the same time progression of cataract occurred in LE, as well as slight progression of the finding on glaucoma perimetry and OCT RNFL. Surgery for complicated cataract was performed on the patient, with postoperative best corrected VA 1.0. Due to persistent elevation of IOP upon a background of mild chronic uveitis, the patient also underwent YAG goniopuncture without any greater effect, and subsequently a further antiglaucoma procedure, specifically implantation of a Preserflo® drainage implant. No satisfactory reduction of IOP was achieved, and due to slight progression on OCT of RNFL, reimplantation of a Preserflo® implant with mitomycin was performed. Up to the present time the patient has compensated IOP without antiglaucoma therapy, and due to the chronicity of the condition maintains long-term use of ganciclovir 0.15% gel 2x per day and dexamethasone 2x per day, without further recurrence of uveitis.

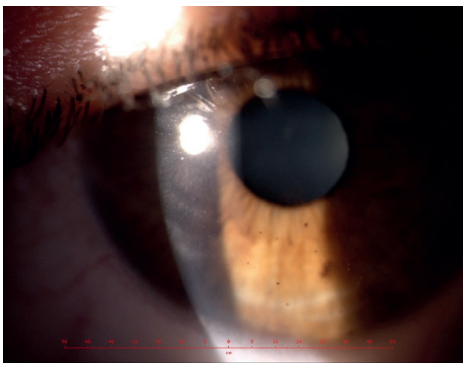

Figure 5. Pigmented precipitates and pigment dispersion in the center of endothelium (less visible), subepithelial lesions of cornea

Patient no. 3, a man aged 67 years, was referred to our center due to suspected PSS in RE. He had suffered attacks previously, and his present attack was without regression of the complaints even after the administration of local therapy with dexamethasone 5x per day and timolol 2x per day. At our examination mild anterior uveitis was present in RE, with medium-sized whitish precipitates on the corneal endothelium and typical plaque of endotheliitis, in the anterior chamber cells 1+ (Figure 6), on the fundus there was evident asymmetry of excavations of the optic disc, in RE C/D 0.6, in LE C/D 0.3. On glaucoma perimetry nasal scotoma was present in RE. Due to suspected CMV etiology, ganciclovir 0.15% gel was administered locally 5x per day, dexamethasone was increased to 5x per day, and antiglaucoma therapy increased to a combined preparation of timolol and dorzolamide. Remission of uveitis and compensation of IOP was achieved in the patient, progressively with regression of endotheliitis. After reduction of ganciclovir and dexamethasone to a prophylactic dose of 2x per day the patient was in remission for several months, but then there was reactivation of uveitis and elevation of IOP to 40 mmHg. Despite maximum antiglaucoma therapy a slight progression of the changes occurred on glaucoma perimetry and OCT RNFL in RE. As a result, deep sclerectomy with 360° trabeculotomy with mitomycin was performed on the patient, and a sample of the aqueous humor for PCR diagnosis, with CMV positivity. Hyphema was present in the anterior chamber with very slow resorbtion, at a follow-up examination in artificial mydriasis we recorded closure of the chamber angle. As a result surgical iridectomy was performed with lavage of the anterior chamber. For several months the patient has been on prophylactic therapy

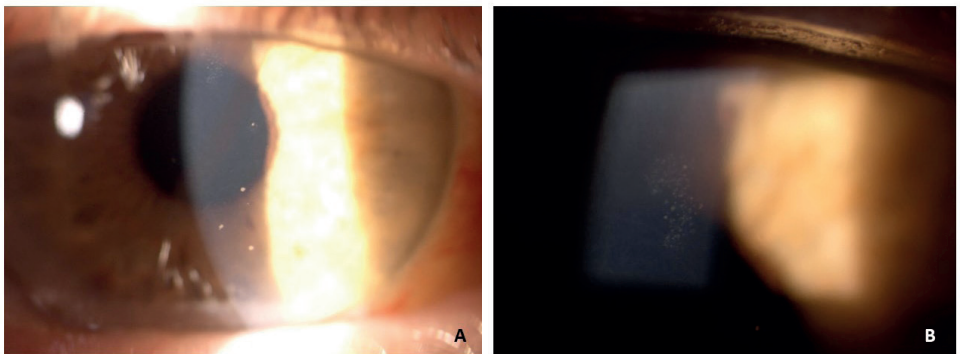

Figure 6. Patient no. 3: (**A**) Anterior segment in activity – eye without injection, medium sized white keratic precipitates in the center end lower part of endothelium and typical coin-shaped lesion in upper part of cornea. (**B**) Coin-shaped keratic precipitate in detail

with ganciclovir 0.15% gel and dexamethasone 2x per day, with best corrected VA of 1.0 without recurrence of uveitis and compensated IOP without therapy.

DISCUSSION

In the countries of Western Europe and North America, CMV anterior uveitis is most commonly manifested as acute recurrent hypertensive anterior uveitis with gradual transition to chronicity, which also corresponds to the course in our patients. A typical picture attesting to the presence of CMV is endotheliitis with a characteristic finding of coin-shaped lesions, which was present in all our patients. In two of them rare clinical manifestations also appeared, namely subepithelial corneal lesions and dilation of the pupil with slow reaction upon activity of the disease. In patient no. 2 disperse of pigment on the endothelium was also recorded during the course of the disease, which is associated with higher recurrence of attacks of uveitis [11]. In patient no. 1 less usual bilateral affliction occurred, which is more common in CMV in comparison with typical unilateral occurrence in VZV and HSV. The diagnosis is deduced from the clinical picture, and exact verification is with the aid of PCR examination of the aqueous humor. However, positivity may not always be confirmed due to the low viral load in the aqueous humor upon a longer duration of the disease or after the commencement of antiviral therapy. For this reason, a negative PCR result does not exclude this diagnosis [3,4,8]. In all our patients we took a sample of the aqueous humor for PCR analysis during the course of the surgical procedure due to complications of the primary pathology, with a positive result for CMV. It is ideal to perform the sample by puncture of the anterior chamber already upon suspicion of this clinical unit in order to ensure the most timely possible verification of the etiological agent and commence adequate therapy, which will reduce the risk of development of complications. Therapy consists in the administration of ganciclovir locally in the form of gel or drops, or intravitreally, or valganciclovir orally systemically according to the available studies. In the Czech Republic general oral therapy with valganciclovir is currently limited to the specializations of hematology, oncology, infectious medicine and pneumology for patients with immune deficiency, and no intravitreal ganciclovir preparation is available or mentioned. On our patients the therapy available in this country was used, namely ganciclovir 0.15% gel locally, in the acute phase 5x per day, progressively reduced and increased according to the course of the disease. It was maintained for all patients in low prophylactic doses of 1–2x per day. The most effective therapy described in the literature, mainly upon ongoing endotheliitis, is a combination of oral valganciclovir with local ganciclovir 0.15% gel. However, upon oral administration of virostatics alone there was not a significant difference in effectiveness. In comparison with general therapy, locally administered ganciclovir is more effective in prophylaxis of recurrence and has a sufficient therapeutic effect in the acute phase at a dose of 5x per day, in the case of ongoing endotheliitis 6–8x per day [4,5,18]. Long-term prophylactic therapy in small doses is recommended to reduce recurrence of the disease. It is evident from observation of our patients that a dose of ganciclovir 2x per day is sufficient to reduce relapses of inflammation and to control IOP. Another essential component of therapy in the acute phase is locally administered anti-inflammatory preparations, in our patients dexamethasone was administered with an intensity depending on the ongoing inflammation, from 1 to 5 drops per day. Upon elevation of IOP in the patients, local antiglaucoma therapy was applied, but this was not sufficient. Even upon maximum therapy a fluctuation of pressure occurred, and ultimately persistent elevation of IOP. For this reason an antiglaucoma procedure was performed on all patients. Trabeculectomy was performed in the first line on two patients. In the case of patient no. 2, due to failure of the trabeculectomy we proceeded in the second phase to implantation of a Preserflo® drainage implant, and when this failed, we implemented reimplantation with mitomycin in order to reduce the risk of scarring and loss of functionality of the implant. According to the literature, minimally invasive glaucoma surgery (MIGS) procedures may be performed in the first line, in which the choice depends on the surgeon. Long-term data is not yet available. From the long-term perspective, filtration operations with mitomycin, above all trabeculectomy and drainage implants, remain the gold standard for compensation of IOP [4,10]. Secondary uveitic glaucoma, frequently also with a steroid component, is the most common complication in CMV anterior uveitis, requiring a surgical procedure in almost 50% of cases [4,13,16]. Another common complication is the development of complicated cataract. A rare complication is corneal decompensation due to ongoing endotheliitis, with the necessity of corneal transplantation. An appropriate supplementary examination in the case of endotheliitis is monitoring of the number of endothelial cells with the aid of an endothelial microscope, or anterior segment OCT [14,15]. These examinations were not performed on our patients, and even despite ongoing endotheliitis none of them suffered corneal decompensation.

CONCLUSION

CMV anterior uveitis is rare in our geographical region, but it is necessary to consider this unit due to the potential development of sight-threatening complications. The course itself, most frequently manifested in recurrent attacks of mild unilateral anterior uveitis with high elevation of IOP in the acute phase, minimal or no affliction of the iris without posterior synechiae, responding insufficiently to anti-inflammatory treatment, should guide us towards a correct diagnosis. The presence of endotheliitis with typical coin-shaped lesions is pathognomonic for this unit and concerns a significant predictive factor for CMV etiology. Timely verification of the etiological agent with commencement of commensurate antiviral and anti-inflammatory therapy is crucial with regard to the further prognosis of the pathology

and the development of complications. Low maintenance doses of topically administered ganciclovir for a period of several months to years prevent frequent relapses of anterior uveitis and decompensation of IOP. CMV anterior uveitis is a relatively rare pathology, for which precise procedure regarding the dosing and length of therapy have not been stipulated to date. Only the results of future clinical trials on larger cohorts of patients can contribute to a standardization of the diagnosis and treatment of this type of uveitis.

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