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CLINICAL INVESTIGATION

Relationship between the number of cytomegalovirus in anterior chamber and severity of anterior segment inflammation

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Abstract
Purpose To characterize the cytomegalovirus-associated anterior segment inflammation and to determine whether the number of cytomegalovirus is significantly correlated with the disease characteristics.
Methods Retrospective consecutive case series. Seventy-three patients with refractory anterior segment inflammation due to iridocyclitis, corneal endotheliitis and keratouveitis were studied. All the patients were suspected to have cytomegalovirus infection and had undergone real-time PCR of the aqueous humor to determine the amount of cytomegalovirus DNA.
Results Cytomegalovirus DNA was detected in 24 of the 73 cases. The cytomegalovirus copy number was significantly correlated with the number of recurrent episodes and glaucoma treatment levels, but was not significantly correlated with the disease type. A high cytomegalovirus copy number was a significant risk factor for IOP elevation [Odds ratio (OR) per logarithm CMV amount: 2.5 (95 % confidence interval (CI) 1.1–5.4), presence of coin-shaped lesions (2.3 (1.3–4.0)), recurrent inflammation (2.1 (1.3–3.5)), and reduction of endothelial cell densities (1.7 (1.2–2.5))]. An IOP elevation [OR 18.2 (95 % CI 2.2–153.0)], reduction of endothelial cell densities [13.2 (2.9–60.0)], and recurrent inflammations [11.9 (2.5–56.6)], but not the disease type, were significant predictors of the presence of $>10^3$ copies/ml cytomegalovirus in the aqueous.
Conclusions Measurements of the cytomegalovirus DNA amount is useful for evaluating the severity of the anterior segment inflammation.

Keywords Cytomegalovirus · Real-time PCR · Endotheliitis · Iridocyclitis

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Introduction

Inflammatory diseases of the anterior segment are manifested by cells and flare in the anterior chamber both with and without keratic precipitates, elevated intraocular pressure (IOP), and loss of corneal endothelial cells. The course of the disease can be acute or chronic, and it can recur. A well-known example of an acute anterior segment disease is the Posner–Schlossman syndrome, and that for chronic anterior segment disease is Fuchs heterochromic iridocyclitis [1]. The etiology of Posner–Schlossman syndrome, Fuchs heterochromic iridocyclitis and other related anterior segment inflammations remains mainly undetermined.

Corneal endotheliitis, one type of anterior segment inflammation that presents as inflammation of the corneal endothelium, is characterized by corneal edema either with or without anterior chamber inflammation, keratic precipitates and elevated IOP [2, 3]. Corneal endotheliitis can be acute or chronic, frequently recurs and responds poorly to corticosteroid therapy.

Recent studies show that infections by the herpes family of viruses, including herpes simplex virus, varicella-zoster virus and human cytomegalovirus (CMV), are important causes of corneal endotheliitis [4–6]. Of these, the ubiquitous lymphotropic herpes virus, CMV, has been shown to be the causative agent of the rare vision-threatening CMV retinitis found in immuno-compromised hosts [7]. CMV is

also reported to be associated with anterior segment inflammation in eyes with iridocyclitis or endotheliitis [1, 6, 8–10]. In immune competent subjects, the DNA of CMV has been detected in the aqueous humor of eyes with anterior uveitis [1, 9, 11, 12] and corneal endotheliitis by polymerase chain reaction (PCR) [6, 8, 10, 13, 14].

These findings suggest that, whenever CMV is present in the aqueous humor, anterior uveitis and corneal endotheliitis belong to the same spectrum of disease categories. However, the relative role of CMV infections in the etiology and parameters of the disease is not well understood. Moreover, determining the amount of CMV by real-time PCR is not a routine procedure in most referral hospitals. Thus, we do not have enough information on the prevalence of CMV infections in cases of anterior segment inflammations when the initial screening examinations do not give definitive results.

The purpose of this study was to evaluate the effects of CMV infection on the clinical features of anterior segment inflammation, including iridocyclitis and endotheliitis. These features were compared to the amount of the DNA of CMV that was present in the aqueous humor as determined by real-time PCR.

Materials and methods

Patients

The medical records of 93 eyes of 73 consecutive patients with iridocyclitis, keratouveitis or corneal endotheliitis, who were suspected of having CMV infection and had undergone real-time PCR of the aqueous humor for CMV, were reviewed. All of the eyes studied were distinguished by frequent inflammation episodes which were not resolved by topical steroids. Thirty-nine of the 73 patients were men, and the mean age of all the patients was 61.2 ± 1.7 years. Sixty eyes of 48 patients were diagnosed with iridocyclitis, 6 eyes of 5 patients with keratouveitis, and 27 eyes of 20 patients with corneal endotheliitis.

The 73 patients were examined at the Tottori University Medical Hospital between November 2005 and March 2011. For control, 26 healthy subjects without any ocular inflammation who were scheduled to undergo routine cataract surgery were studied. Eyes with ocular surface or posterior segment diseases were excluded.

Before collecting the aqueous humor samples, patients underwent routine examinations to try to determine the causes of the anterior uveitis. Cases with infections of herpes simplex virus or varicella zoster virus as determined by real-time PCR of the aqueous humor samples were excluded [4]. In addition, systemic examinations were performed to determine if systemic inflammatory disorders, infectious diseases, or neoplastic diseases were the cause of the diseases. Cases with defined etiology were also excluded from the analysis.

This retrospective study was approved by the Institutional Review Board of Tottori University, Tottori, Japan. All invasive procedures conformed to the tenets of the Declaration of Helsinki and were prospectively approved by the same committee. Informed consent was obtained prior to the procedures from all of the participants after explanation of the procedures to be used.

Real-time PCR

The aqueous humor was collected by paracentesis, and DNA was extracted from the aqueous humor with the QIAamp DNA mini kit (Qiagen, Hilden, Germany) [4]. The glycoprotein B gene of CMV was amplified with the LightCycler (Roche, Basel, Switzerland) as described [15]. A standard curve was generated with known dilutions of genomic DNA as described [16]. Based on the reproducibility of the known amounts of DNA, samples with less than 10 copies/ml in the aqueous humor were considered negative.

Clinical parameters of eyes with CMV-associated anterior segment inflammation

To characterize the clinical parameters of eyes with refractory anterior segment inflammation, the parameters were graded to determine whether they were significantly associated with the copy numbers of CMV. The parameters tested were: more than three recurrent inflammation episodes, IOP elevation to >21 mmHg without glaucoma medication, unilateral corneal endothelial cell loss to <1000 cells/mm^2 or less than 500 cells/mm^2 of the contralateral non-inflamed eye, history of keratoplasty, coin-shaped lesions (circularly arranged keratic precipitates), type of the disease (iridocyclitis, endotheliitis, or keratouveitis) and duration of the disease.

The maximum CMV copy number detected during the course of the disease was classified into 6 groups: 0, none detected; 1, >10 but $\leq 10^3$; 2, $>10^3$ but $\leq 10^4$; 3, $>10^4$ but $\leq 10^5$; 4, $>10^5$ but $\leq 10^6$; and 5, $>10^6$ copies/ml. The degree of glaucoma was classified into 5 groups according to the number and type of glaucoma medications: 0, no medication: 1, 1 topical medication; 2, 2 topical medications; 3, 3 topical medications (β blocker, prostaglandin analogue, and carbonic anhydrase inhibitor) and 4, oral medication or glaucoma surgery [17]. These parameters were used to determine whether they were significantly correlated with the CMV DNA copy number in the aqueous humor by Spearman correlation analysis.

Statistical analyses

Data are presented as the mean ± standard error of the means (SEMs). For bilateral cases, the more severely affected eye was statistically analyzed. To evaluate the significance of the difference between groups, unpaired *t* tests or Mann–Whitney *U* tests were used. Logistic regression analysis was carried out to compute the odds ratios (OR). $P < 0.05$ was considered significant.

Results

Real-time PCR was used to determine whether CMV DNA was present in the aqueous humor of eyes with the refractory anterior segment inflammation and suspected to have CMV infection. The DNA of CMV was detected in 24 of the 73 cases (32.9 %). Of these, 16 were men and 8 were women, and their mean age was 59.2 ± 2.8 years. The mean age of the CMV-negative cases was 62.1 ± 2.2 years ($P = 0.44$).

In the 24 CMV-positive eyes, 15 had iridocyclitis, 8 had corneal endotheliitis and 1 had keratouveitis. The mean CMV copy numbers were $5.8 \times 10^5 \pm 3.8 \times 10^5$ copies/ml for eyes with iridocyclitis and $6.9 \times 10^5 \pm 3.9 \times 10^5$ copies/ml for eyes with endotheliitis (Fig. 1). This difference in copy numbers was not significant.

We also determined whether healthy subject had CMV in the aqueous humor because the anti-CMV antibody titer is reported to be positive in more than one-half of elderly subjects [17]. When the aqueous of 26 patients undergoing routine cataract surgery (mean age 70.1 ± 2.3 years) was tested for CMV copy numbers by real-time PCR, no CMV DNA was detected.

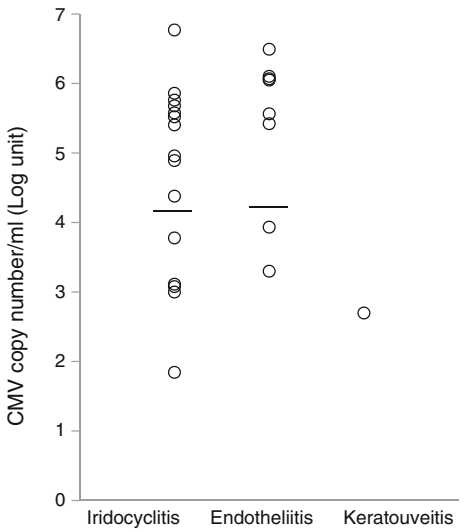

Fig. 1 Examinations for CMV DNA in the anterior chamber of eyes with anterior segment inflammation of unknown etiology. CMV DNA was detected in 15 cases of iridocyclitis, 8 cases of endotheliitis, and 1 case of keratouveitis. *Bars* indicate the mean copy numbers in each group. The difference in the CMV DNA copy numbers between the iridocyclitis and endotheliitis cases was not significant

Association of clinical parameters with CMV-associated anterior segment inflammation

In all the 73 cases of refractory anterior segment inflammation, the presence of DNA of CMV in the aqueous was significantly associated with the presence of an elevated IOP (>21 mmHg) ($P = 0.006$) and the presence of coin-shaped lesions ($P = 0.0002$, Fisher exact test, Table 1). The presence of DNA of CMV was also significantly associated with more than three recurrent episodes of inflammation ($P = 0.005$, Fisher exact test), and a reduction of the corneal endothelial cell density ($P = 0.02$, Fisher exact test). In addition, the duration of the inflammation was significantly longer (144.4 ± 25.8 months) in the cases with CMV DNA than in the cases without CMV DNA (84.8 ± 13.7 months, $P = 0.03$) in the aqueous. Neither the type of disease nor a history of keratoplasty was significantly associated with the presence of CMV.

We examined whether the copy number of CMV in the aqueous of eyes with refractory anterior segment inflammation was quantitatively related to the clinical parameters using Spearman correlation analysis. The CMV DNA copy number was significantly associated with the number of recurrences (correlation coefficient, $\rho = 0.987$, $P = 0.0001$; Fig. 2a). The CMV DNA copy number was also significantly associated with the glaucoma treatment groups ($\rho = 0.561$, $P = 0.0002$; Fig. 2b).

Logistic regression analysis of CMV DNA copy numbers and morbidity parameters

Logistic regression analyses were used to determine the relationship between the copy numbers of CMV DNA in the aqueous humor and the IOP elevation, corneal endothelial cell density reduction, number of recurrent inflammations, and presence of coin-shaped lesions. In the 73 cases with refractory anterior segment inflammation, the CMV DNA copy number had significant odds ratios for all of these parameters (Table 2).

The highest OR was found for the IOP elevation [OR = 2.5 per category, $P = 0.02$, 95 % confidence interval (CI) 1.1–5.4, after age adjustment]. The presence of coin-shaped lesions had the second highest OR (OR = 2.3 per category, $P = 0.002$, 95 % CI 1.3–4.0, after age adjustment) followed by the number of recurrent inflammation episodes (OR = 2.1 per category, $P = 0.003$, 95 % CI 1.3–3.5, after age adjustment) and the corneal endothelial cell density reduction (OR = 1.7 per

Table 1 Association of clinical parameters with CMV-DNA

	Elevated IOP (>21 mmHg)**		The presence of coin-shaped lesions****		Recurrent episodes of inflammation***		Reduction of the corneal endothelial cell density*		History of keratoplasty		Type of the disease		
	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	Iridocyclitis	Endotheliitis	Keratouveitis
CMV DNA positive	22	2	7	17	20	4	17	7	5	19	15	8	1
CMV DNA negative	29	20	0	49	23	26	20	29	6	43	33	12	4

* $P = 0.02$, ** $P = 0.006$, *** $P = 0.005$, **** $P = 0.0002$

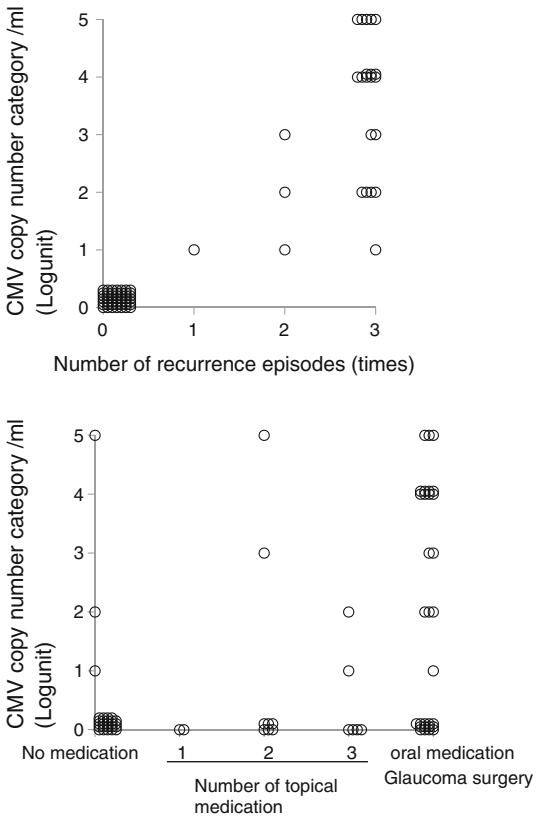

Fig. 2 Correlation between maximum amount of CMV DNA and number of recurrences and anti-glaucoma treatment categories. **a** Correlation between the maximum CMV DNA amount and number of recurrences. Inflammatory events increases significantly with an increase in the CMV DNA copy numbers (correlation coefficient = 0.987, $P = 0.0001$). Log CMV copy number: 0, none detected; 1, >10 but $\leq 10^3$; 2, $>10^3$ but $\leq 10^4$; 3, $>10^4$ but $\leq 10^5$; 4, $>10^5$ but $\leq 10^6$; and 5, $>10^6$ copies/ml. **b** Correlation between the maximum CMV DNA amount and anti-glaucoma treatment categories. Scores of anti-glaucoma treatment significantly increases with an increase in the amount of CMV DNA copy numbers (correlation coefficient = 0.561, $P = 0.0002$). Log CMV copy number: 0, none detected; 1, >10 but $\leq 10^3$; 2, $>10^3$ but $\leq 10^4$; 3, $>10^4$ but $\leq 10^5$; 4, $>10^5$ but $\leq 10^6$; and 5, $>10^6$ copies/ml

category, $P = 0.005$, 95 % CI 1.2–2.5, after age adjustment). Thus, CMV infection affected the IOP elevation, presence of coin-shaped lesion, recurrent inflammation episodes, and corneal endothelial cell loss in these eyes with refractory anterior segment inflammation in a CMV DNA amount dependent manner.

Predicting CMV-associated anterior segment inflammation by IOP elevation, endothelial cell reduction, and number of recurrent inflammation episodes

It is still not known whether the presence of CMV in the aqueous is directly associated with the anterior segment inflammation or is due to a secondary reactivation of CMV by the inflammation. To discriminate between CMV-associated anterior segment inflammation and a possible secondary activation, the requirement of an anti-CMV treatment appeared to be an important parameter. All the CMV positive cases which did not require anti-CMV treatment had $<10^3$ copies/ml (478 copies/ml at maximum).

Therefore, a disease category called "CMV-associated anterior segment inflammation" was created and the were classified as eyes with anterior segment inflammation with $>10^3$ copies/ml of CMV in the aqueous. It is still not known whether the presence of CMV in the aqueous is directly associated with the anterior segment inflammation or is due to a secondary reactivation of CMV by the inflammation.

We then analyzed the characteristics of the eyes classified as "CMV-associated anterior segment inflammation". Of the 73 consecutive cases, 22 cases met the criteria of having $>10^3$ copies/ml of CMV in the aqueous. Logistic regression analysis was then performed on the 73 eyes, and the significantly associated parameters were extracted from the variables, including recurrent inflammation episodes, IOP elevation, corneal endothelial cell reduction, coin-shaped lesions, history of keratoplasty, and disease type.

Of these parameters, the number of recurrent inflammation episodes, IOP elevation, and corneal endothelial cell reduction were significantly associated with $>10^3$ copy number of CMV (Table 3). The highest ORs were for cases

Table 2 Morbidity associated with CMV DNA copy numbers by logistic regression analysis

	Odds ratio of CMV DNA copy numbers					
	Lowest category (CMV not detected)	Positive CMV DNA >10 and ≤1000 copies/ml	95 % confidence interval	Positive CMV DNA >1000000 copies/ml	95 % confidence interval	*P* value
Intraocular pressure elevation (>20 mmHg)	1.0	2.5	1.1–5.4	97.0	2.0–4741.4	0.02*
Coin-shaped lesion	1.0	2.3	1.3–4.0	66.0	4.5–984.0	0.002*
Recurrent inflammation episodes	1.0	2.1	1.3–3.5	40.7	3.4–496.0	0.003*
Corneal endothelial cell loss	1.0	1.7	1.2–2.5	15.3	2.3–102.7	0.005*

CMV DNA copy number was stratified into 5 categories

0, not detected; 1, >10 and ≤1000; 2, ≥ and ≤10000; 3, >10000 and ≤100000; 4, >100000 and ≤1000000; 5, >1000000 copies/ml)

* Statistically significant

Table 3 Clinical parameters associated with "CMV-associated anterior segment inflammation" (defined as 10^3 copies/ml of CMV in the aqueous)

* Statistically significant

Clinical parameter	Odds ratio	95 % confidence interval	*P* value
Intraocular pressure elevation (>20 mmHg)	18.2	2.2–153.0	0.008*
Corneal endothelial cell loss	13.2	2.9–60.0	0.0009*
Recurrent inflammation episodes	11.9	2.5–56.6	0.002*

of IOP elevation and endothelial cell reduction (OR for IOP elevation = 18.2, 95 % CI 2.2–153.0, $P = 0.008$; OR for endothelial cell reduction = 13.2, 95 % CI 2.9–60.0, $P = 0.0009$) followed by the number of recurrent inflammation episodes (OR = 11.9, 95 % CI 2.5–56.6, $P = 0.002$, after age adjustment). No other clinical parameters, including disease type, were significantly associated with this disease category.

Discussion

Earlier studies show that CMV can be detected in cases of anterior segment inflammation, and these cases were usually diagnosed as iridocyclitis or corneal endotheliitis [1, 18, 19]. We classified anterior segment inflammation by the presence of intracameral CMV DNA and analyzed how the CMV DNA amount might be associated with the severity of the inflammation.

An earlier report by Chee et al. [1] shows that the CMV infection in presumed Fuchs heterochromic iridocyclitis eyes was significantly associated with an older age at diagnosis, with men, and with nodular endothelial lesions. Miyanaga et al. [14] show that the reduction in the endothelial cell density was significantly correlated with the intracameral amount of CMV in 11 cases of anterior uveitis. More recently, Hwang et al. [19] reported that an IOP elevation and coin-shaped lesions were significantly associated with anterior segment CMV infection using conventional PCR. In spite of these studies, there is still lack of comprehensive information on how the severity of each clinical feature or other clinical parameters contributed to the etiology of the anterior chamber CMV infection. We suggest that this is because conventional PCR was not always sensitive enough, and could not obtain quantitative values of the copy number of the DNA of CMV [20].

We found that the characteristic signs of CMV-associated anterior segment inflammation were IOP elevation, recurrence of inflammation and reduction in the corneal endothelial cell density. Our quantitative analysis of the amount of CMV DNA by real-time PCR showed that higher copy numbers of CMV were significantly associated with IOP elevation and recurring inflammation (Fig. 2). The significant correlations between the CMV load or presence of CMV genome and the disease severity indicate that the CMV infection was directly involved in the clinical condition of the eyes. Notably, the IOP elevation significantly predicted the presence of CMV (>10^3 copies/ml) with a high OR of 18.2. Thus, clinicians need to be aware that an IOP elevation is the most characteristic feature for CMV infection.

CMV infection of anterior chamber is manifested mainly as either endotheliitis or iridocyclitis [6, 10, 21]. However, how the specific disease type of CMV infection can be diagnosed remains undetermined. Interestingly, the CMV load in eyes with iridocyclitis was not significantly different from that in eyes with endotheliitis. In addition, the type of disease provided no significant risk for presence of CMV. Thus, the difference between the two major forms of inflammation probably reflects not the CMV amount but

what structures infected by the CMV. Interestingly, our earlier study shows that the aqueous level of CMV DNA was $1.2 \times 10^5 \pm 2.1 \times 10^4$ copies/ml for eyes with CMV retinitis ($N = 4$), similar to the levels of CMV DNA in our cases of refractory anterior segment inflammation.

There is an argument that CMV could be spontaneously shed or reactivated in unrelated inflammation which could recruit mononuclear cells to the inflammatory site. However, our preliminary analysis of the amount of intracameral CMV DNA responding to defined anterior chamber inflammations did not detect any CMV DNA ($N = 14$, data not shown).

We found that the amount of CMV DNA was significantly associated with important clinical parameters. In addition, high amounts of CMV DNA appeared to indicate the need to initiate anti-CMV treatment, irrespective of whether CMV is causative or merely associated with the inflammation. For cases of idiopathic and refractory anterior segment inflammation, anti-CMV treatments may need to be considered when frequent IOP elevations, repeated inflammations, or endothelial cell reductions are observed.

For managing CMV-associated with refractory anterior segment inflammations, a definitive diagnosis is crucial. In addition, the amount of CMV DNA in the aqueous is significantly associated with the severity of the disease parameters, including IOP elevation, presence of coin-shaped lesion, recurrent inflammation and reduction of endothelial cell density in a descending order of risks. Without PCR, a proper diagnosis or management of the clinical symptoms is generally difficult. However, accurate risk evaluations using clinical feature profiles is an alternative measure and will be helpful for differential diagnosis for general practitioners not easily accessible to PCR testing.

To summarize, CMV DNA was found in the aqueous humor of about one-third of the refractory iridocyclitis and endotheliitis cases, especially in those with IOP elevation and frequent recurrences. Quantification of intracameral CMV amount by real-time PCR is not only useful for definitive diagnosis of CMV infection, but also for evaluating the disease severity and its management.

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