• Clinical Research •

Risk factors for the long-term prognosis and recurrence of HIV-negative cytomegalovirus retinitis in North China

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Abstract

● **AIM:** To demonstrate the clinical features, the risk factors, the visual prognosis and the recurrence of cytomegalovirus (CMV) retinitis (CMVR) in HIV-negative patients.

● **METHODS:** HIV-negative patients with CMVR were involved in this study. Best corrected visual acuity (BCVA), intraocular pressure (IOP), CMV-DNA load in aqueous and/or serum samples, treatment, follow-up time, recurrence and complications were recorded. Ocular characteristics were evaluated by fundus photographs. Association between ocular factors and visual prognosis were analyzed by regression analysis.

● **RESULTS:** Twenty-five eyes of 16 patients were included. All 25 eyes underwent intravitreal injections of anti-viral agents. The mean logMAR BCVA improved from 0.94±0.98 (0.98-0.78) initially to 0.77±0.73 (0.82-0.68) at last visit, but not significantly. After antiviral treatment, the aqueous CMV DNA load significantly reduced to (3.42±1.47)×10^2 copies/mL (P=0.001), compared with (2.51±3.11)×10^5 copies/mL at baseline. Macular involvement (R^2=0.475, P=0.049) and initial visual acuity (R^2=0.475, P=0.017) were significantly associated with the poor visual prognosis (BCVA<20/400). The extent of retinal lesions (R^2=0.064, P=0.04) was significant associated with the risk of recurrence of CMVR.

● **CONCLUSION:** Intravitreal injection of anti-viral agents offers a safe and effective treatment for CMVR. Macular involvement and initial visual acuity significantly associate with visual prognosis. The extent of retinal lesions is significantly associated with the recurrence of CMVR. These ocular factors can be used as predictive risk factors for long term visual prognosis in HIV-negative CMVR patients.

● **KEYWORDS:** cytomegalovirus retinitis; aqueous humor; visual acuity; risk factors; recurrence

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INTRODUCTION

Cytomegalovirus (CMV) infection is common in immunocompromised patients with human immunodeficiency virus (HIV) infection[1-4]. Cytomegalovirus retinitis (CMVR) is a common cause of blindness in immunocompromised population[5-7]. HIV-negative CMVR is more common in patients with hematologic malignancies[8], who undergo immunosuppressive therapy[9-10], or after organ transplantation[11]. In recent years, the incidence of CMVR after hematopoietic stem cell transplantation (HSCT) is on the rise[12]. With the increase of long-term survival rate of patients after HSCT, CMVR related severe vision loss compromised quality of life in these patients[13-16].

Although several studies reported the clinical features and prognosis of CMVR, most of them focused on HIV-positive patients[17-20]. Researches for the long-term follow-up (more than 6mo) prognosis of HIV-negative CMVR patients were limited. In this study, we demonstrated the clinical features and identify the risk factors that predict the long-term visual prognosis and recurrence of CMVR in HIV-negative patients.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Institutional Ethics Committee of the Beijing Chaoyang Hospital affiliated to the Capital Medical University (2021-7-16-1), The informed

Table 1 General characteristics of the patients

Patient No.	Eye	Age	Gender	Predisposing disease	Medical history	Length of FU (mo)	Last known status/survival status
1	Bilateral	24	F	ALL	6mo after BMT	36	Alive
2	Unilateral	34	M	AML	5mo after BMT	9	Alive
3	Unilateral	20	F	ALL	7mo after BMT	11	Alive
4	Bilateral	9	F	AML	5mo after BMT	11	Alive
5	Unilateral	24	M	AA	6mo after BMT	22	Alive
6	Bilateral	23	M	ALL	5mo after BMT	6	Dead (suicide)
7	Unilateral	43	F	AML	4mo after BMT	21	Alive
8	Unilateral	54	F	Thymoma	16mo after thymectomy	26	Alive
9	Bilateral	31	F	AML	3mo after BMT	25	Alive
10	Bilateral	34	M	AML	7.5mo after BMT	6	Alive
11	Unilateral	31	F	AML	1.5mo after BMT	6	Alive
12	Bilateral	29	M	AML	6mo after BMT	31	Alive
13	Bilateral	20	M	AML	4mo after BMT	32	Alive
14	Bilateral	8.5	M	ALL	5mo after BMT	25	Alive
15	Bilateral	7	M	ALL	2y after last chemotherapy	42	Alive
16	Unilateral	23	F	AA	5mo after BMT	13	Alive

AA: Aplastic anemia; ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; BMT: Bone marrow transplant; FU: Follow-up.

consent was obtained from oral , and the participants did not receive a stipend. It was performed in accordance with the Declaration of Helsinki.

This retrospective, non-randomized study enrolled patients who were diagnosed with CMVR and follow-up at least 6mo in Beijing Chaoyang Hospital of Capital Medical University, from October 2017 to June 2020. All patients were HIV-negative. The diagnosis of CMVR was based on the characteristic clinical features of CMVR and a positive CMV-DNA in the aqueous humor by real-time polymerase chain reaction (PCR).

Detailed clinical and laboratory data, including age, gender, general conditions, follow-up time, best corrected visual acuity (BCVA), intraocular pressure (IOP), anterior chamber manifestations, retinal lesions, CMV-DNA load in aqueous and/or blood samples, treatment, recurrence and complications were recorded. BCVA was measured using Snellen chart and converted to logMAR. A value of 2.6 logMAR units was assigned for visual acuity (VA) of count fingers (CF), 2.7 logMAR units for hand movement (HM), 2.8 logMAR units for light perception (LP), and 2.9 logMAR units for no light perception (NLP)[21].

Those with VA between 20/70 and 20/400 were defined as moderate to severe visual impairment, while those with VA less than 20/400 were defined as blindness. According to the previous studies of CMVR, the extent of retinal lesion was categorized into 4 groups: Group 1, <10%; Group 2, 11%-25%; Group 3, 26%-50%; and Group 4, >50%[22]. Vitreous haze was divided into 5 grades according to the degree of turbidity: 0, without vitreous opacity; 1, mild vitreous opacity and visible retinal vessels; 2, visible optic disc and blurry vessels; 3, blurry optic disc, unclear boundaries, and invisible retinal vessels; and 4, non-visible optic disc[23]. Retinal vasculitis was identified by vascular sheathing with fuzzy border. Recurrence of retinitis was defined as the appearance of new lesion of any size after the initial retinitis had been resolved.

Statistical analysis was performed using SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA). The data with normal distribution were presented as the mean±SD. All *P*-values were 2-sided and were considered statistically significant when the values were less than 0.05. Factors that might predict the final VA and the recurrence were evaluated in univariate logistic regression analyses. If there was more than 1 factor associated with *P* value <0.05 in univariate level, the factors would be entered into a multivariate logistic regression model.

RESULTS

Characteristics of the Patients In this study, 25 eyes of 16 patients were enrolled. The mean age of patients at presentation was 25.91±12.42y (range: 7-54) and 8 of them were male (50%). Seven patients had unilateral involvement and nine had bilateral involvement. The underlying diseases were 15 cases of hematologic malignancies (93.75%), one case of post-thymectomy (6.25%), 14 cases of post-bone marrow transplantation (87.5%) and one case of post-chemotherapy (6.25%). Except for one case who committed suicide (6.25%) after 6mo of follow-up, the remaining patients were followed for at least 6mo. The mean follow-up time was 20.13mo (range 6-42, median: 21.5). The characteristics of the patients are listed in Table 1.

Macular Involvement and Initial Visual Acuity Significantly Associated with Visual Prognosis The mean logMAR BCVA improved from 0.94±0.98 (0.98-0.78) initially to

0.77±0.73 (0.82-0.68) at last visit, but not significantly (P=0.07). Moderate and severe visual impairment were found in 25% eyes, and 28% of eyes were of blindness. IOP did not vary significantly before (16.22±6.41 mm Hg) and after (13.5±4.65 mm Hg) treatment (P=0.08). Anterior segment signs included anterior chamber cells (48%), keratic precipitates (52%; Figure 1A), and raised IOP without posterior synechiae (higher than 21 mm Hg, 4%). The majority of eyes had an extent of 11%-50% retinal area involvement (16 eyes, 64%; Figure 1B-1D), and retinal vasculitis (21 eyes, 84%; Figure 1E). Four eyes had macular involvement; 3 eyes had disc involvement (Figure 1F). Summary of clinical features of all involved eyes was presented in Table 2.

Through regression analysis, 6 factors including extent of fundus lesions, macular involvement, disc involvement, vitreous haze, retinal vasculitis, and initial VA could explain 47.5% of the final VA. Macular involvement (R^2=0.475, P=0.049) and initial VA (R^2=0.475, P=0.017) were significant associated with the final VA (Table 3).

Aqueous CMV DNA Load Significantly Reduced after Treatment All patients underwent intravitreal injection of anti-CMV agents (Ganciclovir and Foscarnet, Bejing science sun pharmaceutical co., Ltd, China) on a regular basis (once a week, ganciclovir 3 mg; foscarnet 2.4 mg), except one patient underwent only two intravitreal injections for the reason of compliance. The mean duration of treatment was 8.77±9.36wk (range: 2-44.7), and the mean number of injections was 5.32±2.41 (range: 2-12).

PCR was used to detect the aqueous CMV-DNA load. The mean inital aqueous CMV DNA load was $(2.51\pm3.11)\times10^5$ (3.22×10^2-1.04×10^6) copies/mL. After treatment, it reduced significantly to a mean viral load of $(3.42\pm1.47)\times10^2$ (0-5.99×10^2) copies/mL (P=0.001). The prevalence of CMV-DNA in the aqueous humor was 100%. Blood sample was taken from 11 patients for CMV-DNA detection. Among them, 5 patients were positive (45.5%). The initial aqueous CMV-DNA load viral load was not significantly associated with the number of injections (R^2=0.0195, P=0.506). Laboratory data and treatment outcome of all involved eyes were listed in Table 4.

Extent of Fundus Lesions Significantly Associated with the Recurrence of CMVR Among 25 eyes, 2 eyes (8%) suffered recurrence of CMVR during the follow-up. The duration from the regression of primary retinitis to the recurrence was 16 and 8wk, respectively. With the analysis of regression, we found that the duration of treatment, the number of intravitreal injections, the extent of fundus lesions, and the presence of vitreous haze could explain 6.4% of retinitis recurrence, among which the extent of fundus lesions has a significant association with the recurrence of CMVR (R^2=0.064, P=0.04).

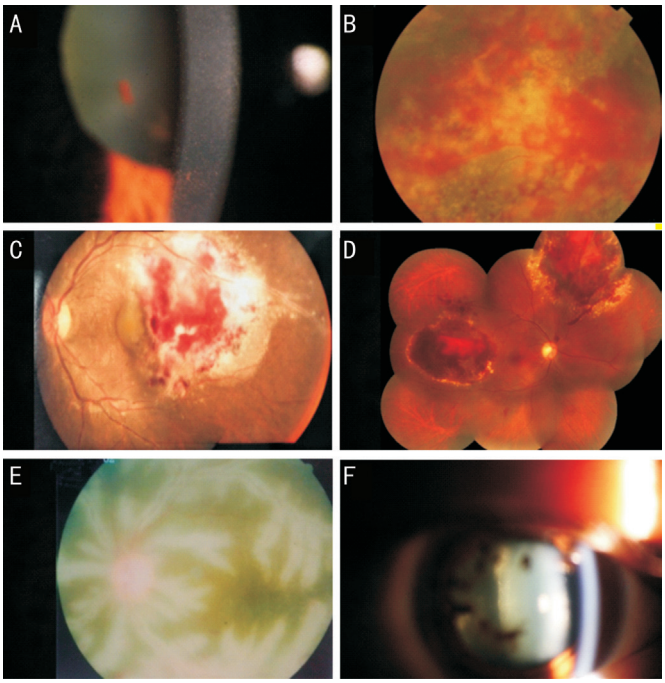

Figure 1 Fundus photographs showing different clinical features of CMVR as follows A: Pigmentary and dust-like keratic precipitates in a 54-year-old female patient; B: Extensive hemorrhage and exudation of the right eye with a cheese-ketchup-like appearance in a 9-year-old female patient; C: Macula hemorrhage, exudation, vascular sheathing of retinal vessels in a 20-year-old female patient; D: Retinal hemorrhage and exudates in a 31-year-old female patient; E: Diffuse vasculitis, frost-like branches in a 8.5-year-old male patient; F: Disc and macular involvement in a 23-year female patient. CMVR: Cytomegalovirus retinitis.

Table 2 Summary of clinical features of all involved eyes

Clinical features	No. of eyes (n=25)	Percentage (%)
Anterior segment manifestations		
Anterior chamber cells	12	48
Keratic precipitates	13	52
Posterior synechiae	0	0
Elevated IOP >21 mm Hg	1	4
Extent of lesion		
<10%	5	20
11%-25%	8	32
26%-50%	8	32
>50%	4	16
Vitreous haze		
0	18	72
1+	5	20
2+	2	8
3+	0	0
4+	0	0
Other features		
Disc involvement	3	12
Macular involvement	4	16
Retinal vasculitis	21	84

IOP: Intraocular pressure.

Table 3 Univariate and multivariate regression analyses of the predictive factors for the final visual acuity

Parameters	Coefficients			*t*	*P*
	Unstandardized coefficients		Standardized coefficients		
	Mean	Standard deviation			
Constant	-0.027	0.404		-0.067	0.947
Extent of lesions[a]	0.259	0.163	0.353	1.586	0.130
Macular involvement	0.706	0.334	0.359	2.110	0.049[b]
Disc involvement	-0.324	0.415	-0.146	-0.779	0.446
Vitreous haze[c]	-0.251	0.225	-0.218	-1.117	0.279
Retinal vasculitis	-0.305	0.340	-0.156	-0.898	0.381
Initial visual acuity	0.430	0.163	0.574	2.629	0.017[b]

Adjusted *R* square=0.475; [a]Every group-unit increase from Groups 1 to 4; [b]Statistically significant with $P<0.05$; [c]Every grade-unit increase from grade 0 to 4.

Table 4 Laboratory data and treatment outcome of all involved eyes

Patient No.	Eye	Aqueous CMV[a] load	Blood CMV[a] load	Intravitreal anti-CMV therapy			Ocular outcome	Complication
				Types of therapy	Duration (wk)	No. of injections		
1	Right	+	—	GCV→FOS	4	5	Remission	ME, VH
	Left	+		GCV→FOS	10.9	9	Remission	ME
2	Left	+	N/A	GCV+FOS	6.9	5	Remission	Nil
3	Left	+	N/A	GCV+FOS	18.7	12	Remission	Nil
4	Right	+	N/A	GCV	8.7	5	Remission	RD
	Left	+		GCV	8.7	5	Remission	RD
5	Left	+	—	GCV+FOS	2.9	4	Remission	Nil
6	Right	+	N/A	GCV	4	4	Remission	Nil
	Left	+		GCV	4	4	Remission	Nil
7	Left	+	—	GCV	2.3	4	Recurrence	Nil
8	Right	+	N/A	GCV+FOS	44.7	9	Remission	RD
9	Right	+	—	GCV	1.9	2	Remission	Nil
	Left	+		GCV	1.9	2	Remission	Nil
10	Right	+	—	GCV+FOS	9.9	5	Remission	Nil
	Left	+		GCV+FOS	11.4	9	Remission	Nil
11	Left	+	—	GCV→FOS	23	6	Remission	VH
12	Right	+	—	GCV	11.9	6	Recurrence	Nil
	Left	+		GCV	11.9	6	Remission	Nil
13	Right	+	—	GCV	2	3	Remission	Nil
	Left	+		GCV	14.1	8	Remission	Nil
14	Right	+	—	GCV+FOS	3	4	Remission	RD, VH
	Left	+		GCV+FOS	3	4	Remission	RD
15	Right	+	—	GCV, FOS	3.6	5	Remission	VH
	Left	+		GCV+FOS	2.9	3	Remission	RD
16	Left	+	—	GCV+FOS	2.9	4	Remission	Nil

CMV: Cytomegalovirus; FOS: Foscarnet; GCV: Ganciclovir; ME: Macular edema; N/A: Not available; RD: Retinal detachment; VA: Visual acuity; VH: Vitreous hemorrhage; —: Negative; +: Positive; →: Followed by. [a]Polymerase chain reaction analysis for CMV DNA in aqueous humor/blood.

Complications Six eyes from 5 patients developed retinal detachment (24%). One patient had bilateral retinal detachment (Patient 14) and underwent pars plana vitrectomy, laser photocoagulation, and silicone oil tamponade. This patient received bilateral silicone oil removal 12mo later with retina attached during the whole follow up period. Vitreous hemorrhage occurred in 4 eyes (16%), and subsequently hemorrhage absorption was observed in one eye, secondary retinal detachment was observed in two eyes (Table 4).

DISCUSSION

In this study, all patients were CMV-DNA positive in the aqueous humor, which was higher than the previous reported

(88.9%). Among the 11 patients with blood samples, 5 (45.5%) were CMV-DNA positive. Therefore, our result indicated that aqueous humor sample CMV-DNA detection is more sensitive than blood sample in the diagnosis of CMVR. However, a negative CMV-DNA in the aqueous humor cannot exclude the diagnosis of CMVR. It was reported that a bilateral CMVR patient with CMV positive in one eye and negative in the other eye[24]. The positive rate could be influenced by many factors, such as the extent of lesions, the degree of optic neuropathy and the severity of retinal vascular lesions[25].

Intravitreal injection of antiviral drugs (ganciclovir and/or foscarnet) was an effective treatment for CMVR[26-30]. Our results showed that the average viral load of CMV was $(2.51\pm3.11)\times10^5$ copies/mL before treatment and $(3.42\pm1.47)\times10^2$ copies/mL after treatment, showing a significant difference. But there was no correlation between baseline viral load and the numbers. of injections. It was inconsistent with the previous studies[23]. We considered that such differences might be caused by the individual differences of susceptibility to antiviral drugs among patients. The decision to discontinue the intravitreal therapy was made based on the treatment response: treatment would be continued until all lesions had become inactive or resolved clinically, and the viral load in the aqueous had become negative on PCR. In this study, no systemic antiviral agent was applied for reason that all involved patients were HIV-negative and were in the state of immunosuppression. Local monotherapy is considered safer in post-transplant patients, as myelosuppression may worsen with systemic antiviral therapies[31]. Also, intravitreal injection enables antiviral agents to reach retinal tissue directly and quickly, which is more effective than systemic antiviral treatment[32-33].

Among all involved patients, two suffered the recurrence of CMVR, which was associated with the reactivation of CMV in the eye. CMVR recurred 2mo after discontinuation of treatment in these two patients. Our result indicated that risk factors including the duration of injections, the numbers of injections, the extent of lesions, and the degree of vitreous haze could only explain 6.4% of the CMVR recurrence, but the extent of lesions had a significant impact on disease recurrence (R^2=0.064, P=0.040). Thus, it is of great significance to effectively control the expansion of fundus lesions. The VA prognosis of CMVR was also evaluated. Our result showed that VA did not change significantly after antiviral therapy, which was consistent with previous study demonstrating that the destruction of retinal cell caused by CMVR is irreversible and irreparable even if the lesion becomes inactive[34]. Our data further indicated that six ocular clinical features (macular involvement, disc involvement, vitreous haze, retinal vasculitis, initial VA, extent of lesion) could explain 47.5% of the final changes of vision. Macular involvement and initial VA could significantly affect the final VA. Thus, our data showed that macular involvement and initial VA were two important predictors for the final visual prognosis in CMVR.

After primary infection, CMV remains in the host cells in latent form. The risk of CMV recurrence is dependent on the level of incompetency of the immune system[35-39], manifested as an impairment of T-cell immunity, including the presence and function of CMV-specific cytotoxic T lymphocytes. From the regression analysis, we found that the extent of fundus lesions, and the presence of vitreous haze were related to retinitis recurrence, among which the extent of fundus lesions has a significant association with the recurrence of CMVR. In addition, many references reported different recurrence rate of CMVR in different types of general diseases. The median rate of CMV recurrence in HSCT recipients was estimated as 37% after allogeneic transplant and 12% after autologous transplant, 5% in patients with non-transplant hematological malignancies, 14% in recipients of anti-CD52 therapy, 30% in solid organ transplant recipients, 21% in patients with primary immunodeficiencies, 20% during active replication in HIV-positive patients and 3.3% during antiretroviral therapy, 7% in patients with chronic kidney disease, 0.6% in patients with congenital infection, and 0.6% in neonates with primary infection[35]. The above data showed that recurrence of CMV infection is not only related to the severity of CMVR, but also related to the type of the general disease and the treatment received.

In this study, none of the involved patients received systemic antiviral treatment, such as oral valganciclovir or intravenous ganciclovir, which was proved to be effective in the treatment of CMVR in the previous studies. The reason was that most patients involved in this study had medical history of bone marrow transplant or chemotherapy. These patients were all in the state of myelosuppression and systematic antiviral treatments might aggravate the neutropenia or thrombocytopenia. However, intravitreal use of ganciclovir had a low systemic exposure. Direct intraocular use also had the advantage of achieving therapeutic levels by circumventing the inefficiency of ganciclovir in crossing the blood-retina barrier. In the prvious study, we indicated that the major disadvantage of IVG was its little benefit for the fellow eye with no virus infection, but now we had impression that the progression of lesions in the fellow eye could be controlled well with close follow-up and timely treatment.

This study has some limitations. First, the retrospective design of this study added a potential selection bias. Some detailed information could not be obtained, such as the initial symptoms of the patients, the exact time of disease, the number of blood CD4+ T cells, the degree of immunosuppression and immune

recovery. Second, the majority of the patients were diagnosed as hematologic malignancies, and the results of this study could not be generalized to other immunosuppressed patients, such as patients with primary immunodeficiency. Third, we didn't involve the time of diagnosis and the time to treatment in the analysis due to the lack of data, which was an important limitation as a delay in diagnosis and treatment could result in worse outcome. Finally, this study involved only HIV-negative patients. Further studies with both HIV-positive and HIV-negative patients will be conducted to compare the difference of prognosis between these two groups.

In conclusion, our study showed that aqueous CMV DNA load decreased significantly after intravitreal injection of anti-viral treatment. Intravitreal injection of anti-viral agents offers a safe and effective treatment for CMVR. Macular involvement and initial VA significantly associated with visual prognosis. The extent of retinal lesions was significantly associated with the recurrence of CMVR. These ocular factors could be used as predictive risk factors for long term visual prognosis in HIV-negative CMVR patients.

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