Int Ophthalmol (2019) 39:1709–1715
https://doi.org/10.1007/s10792-018-0991-2

ORIGINAL PAPER

Visual prognosis, clinical features, and predisposing factors in non-HIV patients with cytomegalovirus retinitis

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Received: 15 January 2018 / Accepted: 14 July 2018 / Published online: 20 July 2018

Abstract

Purpose To study the characteristics and visual outcome of cytomegalovirus retinitis in patients of a tertiary referral ophthalmology center.

Methods This retrospective cross-sectional study included 16 patients who presented with CMV retinitis between February 2014 and January 2017. Demographics, clinical signs, course of treatment, and visual and anatomical results were analyzed.

Results Twenty five eyes of 16 patients were included. Eleven (68.8%) were females. The mean age was 29.37 ± 17.12 (range 11–73) years. Involvement was bilateral in 9 (56.2%) cases. HIV serology was negative in all patients. Best-corrected visual acuity was 0.57 ± 0.55 logarithm of the minimal angle of resolution (LogMAR) at the time of presentation and decreased to 0.69 ± 0.55 LogMAR on final visit ($P = 0.332$). None of the patients participating in this study was HIV-positive.

Conclusion CMV retinitis is a devastating complication in immunosuppressed. The visual acuity usually decreases despite aggressive appropriate treatment. This observation supports the increasing incidence of CMV infection in non-HIV patients.

Keywords Cytomegalovirus retinitis · Visual prognosis · Organ transplantation · HIV · Non-HIV

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Introduction

Cytomegalovirus (CMV) is an enveloped double-stranded DNA virus in the Herpesviridae family [1]. Prevalence of latent infection is more than 90% in parts of Africa and Asia [2]. Although the symptomatic ocular involvement is uncommon, CMV retinitis is the most common opportunistic retinal infection and a major sight-threatening complication in profoundly immunocompromised patients [3]. Before the emergence of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), this condition was reported almost exclusively in severely immunosuppressed patients, mostly those undergoing chemotherapy following organ transplantation or malignancy [4–8]. After the advent of AIDS, reports of CMV retinitis in patients without AIDS became unusual, suggesting that AIDS may confer a higher risk of developing CMV retinitis [9]. CMV retinitis follows a systemic viremia and may be a part of disseminated disease including gastroenteritis and nephritis [10–14]. CMV retinitis may exhibit several ophthalmoscopic patterns but usually

starts as a full-thickness necrotizing retinitis in the periphery and progresses centripetally toward the posterior pole [15, 16]. Lesions involving fovea or optic nerve have a significant impact on vision. The aim of the treatment is to arrest the progression of retinitis and preserve as much vision as possible [17].

The most devastating consequences of this condition may be retinal detachment, retinal and extra-retinal neovascularization that may lead to severe visual loss [18, 19]. Treatment consists of strategies aimed at restricting the underlying disease, and systemic and intravitreal anti-CMV medications, but the function of necrotic regions may not be restored [20].

As the different causes of decreased immunity may influence the course and prognosis, we provide a retrospective study on patients with CMV retinitis to clarify underlying disease, clinical course, and visual outcome.

Materials and methods

A retrospective study consisting of 16 patients with CMV retinitis was conducted at Khatam, a tertiary referral eye hospital at Mashhad University of Medical Science, between February 2014 and January 2017. We identified cases of CMV retinitis by reviewing the medical records maintained during this period. This study was approved by the institutional review board of the Mashhad University of Medical Science and was in accordance with the Declaration of Helsinki.

All patients participating in this study were diagnosed with CMV retinitis. The diagnosis was performed based on characteristic fundus lesions detected upon indirect ophthalmoscopic examination (appearance of perivascular creamy whitish retinal infiltration, with or without retinal hemorrhage or peripheral granular retinitis). The diagnosis was further supported by laboratory tests (systemic viremia and/or detection of virus in ocular fluids). Sample of aqueous or vitreous humor was collected from all patients and sent to laboratory for detection of varicella zoster virus (VZV), herpes simplex virus (HSV), and CMV by Polymerase Chain Reaction (PCR). Demographics (age and sex), clinical signs, ocular examination, best-corrected visual acuity (BCVA), medical history including medications, underlying diseases, use of systemic and intravitreal anti-CMV treatment, and ocular complications were extracted from the medical records. Best-corrected visual acuity (BCVA) was measured using a Snellen chart and converted to the logarithm of the minimal angle of resolution (LogMAR) scale for statistical purposes.

Treatment with intravenous ganciclovir (5 mg/kg twice daily) or oral valganciclovir (900 mg, every 12 h) was initiated as soon as the patient was diagnosed, and continued for 2 weeks as the loading dose, and followed by oral valganciclovir (900 mg/day) as maintenance therapy. Intravitreal ganciclovir (2 mg/0.1 mL) was injected twice in the first week and then tapered according to the therapeutic response. In case of any concern regarding drug toxicity, experts were consulted for dose adjustment. Intravitreal therapy was continued until the retinitis became quiescent and scar tissue formation could be observed. The number and interval of injections were based on the location of retinitis lesion and the response to treatment. Patients were instructed to visit the ophthalmology clinic monthly to re-evaluation by measurement of BCVA, intraocular pressure (IOP), complete eye examination, and dilated-pupil ophthalmoscopy. Complications were treated at the time of diagnosis. Systemic treatment with valganciclovir was continued until the reinforcement of immune system, disappearance of retinitis, and complete retinal scarring.

Clinical findings from patients, treatment, and response data were analyzed using descriptive statistics. SPSS software (version 22) was used, and $P < 0.05$ was considered statistically significant.

Results

We identified 20 patients with CMV retinitis between February 2014 and January 2017. Three patients were excluded from the study due to incomplete follow-up. One infant with bilateral CMV retinitis but no identified risk factor was also excluded, for which the results have been reported in a separate case report [21]. A total of 25 eyes from 16 patients with CMV retinitis were treated. Of the 16 patients, 5 (31.3%) were males and 11 (68.8%) were females, and the mean age of patients was 29.37 ± 17.12 years (range 11–73 years). Involvement was unilateral in seven cases (43.8%) and bilateral in nine cases (56.2%). The characteristics of the study population are demonstrated in Table 1.

Out of the 25 eyes treated, 10 (40%) exhibited signs of anterior chamber inflammation such as the presence

Table 1 Characteristics of study patients

Variable	
Sex, *n* (%)	
Men	5 (31.3)
Women	11 (68.8)
Age, years	
Mean (SD)	29.37 ± 17.12
Range	11–75 years
Laterality, *n* (%)	
Unilateral	7 (43.8)
Bilateral	9 (56.2)
Presenting sign, *n* (%)	
AC inflammation	10 (40)
Vitreous cell	13 (52)

of aqueous cells and flare, and keratic precipitates, while 13 out of the 25 eyes (52%) contained vitreous cells.

The mean follow-up period was 7.31 ± 1.95 months (range 6–12) and the mean number of intravitreal ganciclovir injections was 3.44 ± 1.03 (range 2–6) per eye. Although the systemic ganciclovir treatment continued throughout the follow-up period, no adverse effects were observed.

HIV serology was negative in all cases and disseminated CMV disease was not observed in any patients. The diagnosis of CMV retinitis was confirmed by positive PCR results from aqueous or vitreous humor samples obtained from 11 patients; for the remaining patients, diagnosis was based on typical clinical findings.

Regarding the underlying diseases, patients could be classified into distinct groups, including: renal transplant recipients administrated with immunosuppressive agents to prevent rejection [4], patients with acute lymphoblastic leukemia (ALL) undergoing chemotherapy [6], patients with ulcerative colitis [1], patients with T-cell lymphoma undergoing chemotherapy [1], patients with uncontrolled diabetes mellitus [2], and patients with sarcoidosis administrated with immunomodulatory drugs [1]. One of the patients had no risk factor reported in medical history and work-ups. Demographics, background disease, PCR results, treatment course, and visual acuity findings of each patient are presented in detail in Table 2.

The mean LogMAR BCVA at baseline was 0.57 ± 0.55 (Snellen VA, 20/74) and the mean LogMAR BCVA at final visit was 0.69 ± 0.55 (Snellen VA, 20/100) (Table 3).

Patients with ALL were significantly younger than other patients. Mean age was 15.86 ± 4.83 in ALL patients and 37.50 ± 16.73 in others ($P = 0.007$). Bilateral involvement was significantly higher in these patients when compared to other patients (100 vs 30%, p value = 0.008). Other parameters including change of BCVA, number of intravitreal injections, and sex distribution were not significant between ALL patients and others ($P > 0.05$). The same findings of no significant difference between patients with renal transplantation and other background diseased were noted ($P > 0.05$). Similar statistical analyses were not performed for other groups of patients as the small number of members limits the power of statistical analysis.

One patient from the group of renal transplant recipients developed retinal and iris neovascularization and neovascular glaucoma in one eye, 6 months after being diagnosed with CMV retinitis. The visual acuity remained poor despite pars plana vitrectomy (PPV), endolaser, and implantation of Ahmed glaucoma valve (LogMAR BCVA 1.00, Snellen VA 20/200).

Four patients needed barrier laser photocoagulation to stabilize retinal breaks, and one of these patients required PPV, and peeling of epiretinal and internal limiting membrane (ERM and ILM) 3 months later, due to the formation of dense ERM. One patient in the ALL group developed rhegmatogenous retinal detachment (RRD) and was treated with PPV followed by silicone oil tamponade. Retina remained attached, with silicone-filled vitreous cavity on final examination, but the LogMAR BCVA was 1.3010 (Snellen VA, 20/400).

Discussion

An interesting finding in this study is the absence of any HIV-positive patient with CMV retinitis. The prevalence of HIV infection is not clearly determined in north east of Iran. According to the press release, the prevalence of HIV infection is about 750/6,000,000 or 0.01% [22]. This low prevalence may explain the absence of any HIV-positive patient in our series.

Table 2 Demographics, background disease, PCR results, treatment course, and visual acuity findings

No	Age	Sex	Background disease	Laterality	OD visual acuity at baseline (LogMAR) (LogMAR)	OS visual acuity at baseline (LogMAR) (LogMAR)	intravitreal injections (No.)	Follow-up (month)	OD visual acuity at last exam (LogMAR)	OS visual acuity at last exam (LogMAR) (LogMAR)	PCR result	Complication	Surgery
1	37	Female	Renal transplantation	OD	0.60		3	6.0	0.05		NA[a]	NO	NO
2	27	Male	–	OD	0.90		3	6.0	0.60		AC[b]+	NO	NO
3	15	Female	ALL[c]	OU	0.50	0.70	4	7.0	0.50	0.40	AC+	NO	NO
4	23	Male	Renal transplantation	OS		0.80	4	6.0		0.05	NA	NO	NO
5	13	Female	ALL	OU	0.80	0.80	3	8.0	0.40	0.60	NA	NO	NO
6	35	Male	Renal transplantation	OU	0.30	0.10	5	12.0	0.90	0.10	AC+	NVG OS[d]	PPV[e] + Ahmed valve shunt
7	57	Male	Renal transplantation	OD	0.10		3	7.0	0.20		AC+		
8	31	Female	Ulcerative colitis	OU	0.60	0.70	4	10.0	0.02	0.10	AC+		BL[f]
9	73	Female	Diabetes mellitus	OS		0.50	3	6.0		0.10	Vit[g]+	NO	NO
10	26	Female	T-cell lymphoma	OD	1.00		2	6.0	0.50		Vit+	NO	NO
11	46	Female	Diabetes mellitus	OD	0.10		2	7.0	0.30		AC+	ERM	BL, ERM[h] peel
12	15	Female	ALL	OU	0.02	0.02	6	11.0	0.30	0.50	NA	NO	NO
13	20	Male	Sarcoidosis	OU	0.02	0.05	3	6.0	0.02	0.02	AC+	NO	NO
14	25	Female	ALL	OU	1.00	1.00	3	6.0	1.00	1.00	NA	NO	BL OS
15	11	Female	ALL	OU	0.10	0.50	4	6.0	0.10	0.50	Vit+	NO	NO
16	16	Female	ALL	OU	0.20	0.10	3	7.0	0.60	0.02	AC+	ME[i] (OU) RD (OS)	PPV OS

[a]PCR is not performed

[b]Anterior chamber

[c]Acute lymphoblastic leukemia

[d]Neovascular glaucoma

[e]Pars plana vitrectomy

[f]Barrier laser

[g]Vitreous biopsy

[h]Epiretinal membrane peeling

[i]Macular edema

Table 3 Visual acuity at presentation and the last examination

Vision	At presentation, *n* (%)	At the last visit, *n* (%)
20/50≤	14 (56)	12 (48)
20/100 ≤ < 20/50	2 (8)	10 (40)
< 20/100	9 (36)	3 (12)

CMV retinitis is the most common opportunistic retinal infection in severely immunocompromised patients. Acquired immunodeficiency syndrome (AIDS) and chemotherapy performed due to malignancy or organ transplantation may be responsible for occurrence of CMV retinitis in majority of the patients. As the cause of suppressed immunity may differ depending on geographical or cultural regions, we conducted this study to reveal the background, presentation, clinical course, and effect of treatment on visual outcome of patients with CMV retinitis who visited in our ophthalmology center.

We observed that there was no HIV-positive patient in our study population. Acute lymphoblastic leukemia (ALL) or renal transplant recipients were present 10 out of the 16 patients (62.5%).

The increasing incidence of CMV retinitis in HIV-negative patients is mainly related to advancement of chemotherapy used in cases of malignancies, improvement in immunosuppressive therapy, and increased survival of immunosuppressed patients, including transplant recipients treated with immunosuppressive therapy.

More than half of the participants (56.2%) exhibited bilateral retinal involvement. A previous study has reported that 40–65% of patients may present with bilateral involvement, which is similar to our observations [18]. In our study, the majority of patients experienced loss of vision within the follow-up period, despite anti-CMV therapy (pretreatment = 0.57 ± 0.55 [Snellen VA, 20/74]; post-treatment = 0.69 ± 0.55 [Snellen VA, 20/100]). Since there were no HIV-positive patients included in this study, different results might be expected from CMV retinitis in HIV-positive patients. Wagle et al. [23] also reported similar discouraging results, with only 16% of affected eyes showing improvement in vision. Karkhaneh et al. [24] reported an immunocompetent patient with CMV retinitis who exhibited appreciable response to intravitreal ganciclovir.

All patients exhibited visual symptoms such as blurry vision, floaters, or scotoma. Eleven eyes (44%) presented with visual acuity of 20/50 or worse, 9 (36%) of which presented with visual acuity of 20/200 or worse. Kuo et al. [25] reported that one-third of the patients had a visual acuity less than 20/50 at baseline, which is comparable to our findings.

CMV retinitis manifested during the first year after patients were diagnosed with ALL diagnosis or renal transplant in renal transplant recipients. The mean duration ranged from 9 months in this study to more than 1 year in other case studies [26]. Patients received an average of 3.44 ± 1.03 injections of intravitreal ganciclovir per eye during the follow-up period. Intravenous ganciclovir followed by oral medication was prescribed till complete resolution of retinitis and restoration of the immune system observed.

Rhegmatogenous retinal detachment is a serious complication. Gore et al. [27] reported the poor prognosis of retinal detachment in patients with CMV retinitis despite successful surgical results in most cases. One of the patients in our study experienced retinal detachment and the vision remained poor even after complete retinal reattachment by pars plana vitrectomy (PPV) and silicone oil endotamponade (VA = 3 m counting finger). Therefore, it may be necessary to advise regular retinal examination and prophylactic laser treatment or early vitrectomy in case of extensive retinal involvement or retinal break formation.

One of the patients developed retinal and iris neovascularization, and progressed to neovascular glaucoma and profound irreversible visual impairment even after pars plana vitrectomy (PPV), endolaser, and implantation of Ahmed glaucoma device. Retinal ischemia or intraocular inflammations are the events responsible for retinal neovascularization. Although this patient suffered from inflammatory eye disease, the clinical course indicates that the stimulus was retinal ischemia, secondary to vascular occlusions.

Other plausible causes for the absence of HIV-positive patients in this study may be explained by the low prevalence of HIV infection in the region of this study, undiagnosed CMV retinitis, or poor screening of CMV retinitis in HIV-positive patients.

The strength of this study is that it brings new insights into the understanding of causes, clinical course, and visual prognosis in patients of a tertiary ophthalmology clinic. By virtue of its retrospective

design, this also has some limitations. First, medical records were not uniform across patients, due to the retrospective design of study. Second, the relatively small number of cases limited the strength of the statistical analyses. Third, the follow-up was not always standardized and incomplete follow-ups caused by inability of patients to visit the clinic due to deteriorating condition may bias our results.

In conclusion, CMV retinitis is uncommon but serious vision-threatening complication in immune-deficient patients and even with aggressive medical treatment can lead to severe visual impairment and devastating complications. It seems the pattern of CMV retinitis which is changing toward greater incidence in HIV-negative patients. Hence, timely diagnosis and appropriate treatment in immune-deficient or even partially immunocompromised patients may result in more favorable results.

Acknowledgements The authors did not receive any grant support or research funding for this study. This manuscript has been presented as E poster in 27th annual congress of the Iranian society of ophthalmology congress (IRSO) and World Ophthalmology Congress 2018.

Compliance with ethical standards

Conflict of interest The authors have no financial interest in any of the products mentioned in this article.

Human participants and animals statement Our study is a retrospective study and all patient information is confidential, which, therefore, does not include any human participants and/or animals.

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