CLINICAL PROFILES OF CYTOMEGALOVIRUS RETINITIS: 8 YEARS REVIEW

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Abstract. The objective is to describe clinical manifestation and visual outcome of cytomegalovirus (CMV) retinitis. It was a retrospective study where medical records of CMV retinitis patients from January 2011 to December 2018 who were treated at our ophthalmology clinic were reviewed. The data were collected from hospital records. A total of 6 patients (7 eyes) with CMV retinitis were included. There was 66.6% of CMV retinitis patients aged less than 50 years old. There was equal ratio between male and female. All the patients were Malays. Half of the patients has history of hypertension (50.0%). There were 1 patient (16.7%) associated with human immunodeficiency virus (HIV) and 2 patients (33.3%) had diabetes mellitus. All patients presented with blurring of vision and 3 of them (4 eyes, 57.1%) associated with floaters. There were 2 eyes (28.6%) presented with visual acuity worse than 6/60 and 5 eyes (71.4%) had vision better than 6/18. Posterior uveitis comprises 57.1% (4 eyes) compared to 42.9% for panuveitis (3 eyes). Vitritis (7 eyes, 100.0%) and retinitis (6 eyes, 85.7%) were the most common presentation. Three patients received intravitreal ganciclovir alone while 2 patients received combination of intravenous and intravitreal ganciclovir. Only 1 patient received intravenous ganciclovir monotherapy. Four eyes had static vision and 1 eye had vision improvement from 6/15 to 6/6. Overall, 4 eyes (57.1%) had vision better than 6/18 post treatment. CMV retinitis were common among immunocompromised status and can present as posterior uveitis or panuveitis. Visual acuity shows variable results following treatment.
Keywords: *cytomegalovirus, retinitis, human immunodeficiency virus, vitritis*

Introduction

Cytomegalovirus (CMV) is a double stranded deoxyribonucleic acid (DNA) enveloped virus with icosahedral capsid from Herpesviridae group. It contains intranuclear inclusion bodies and multinucleated giant cells. CMV infection is specific to humans and does not infect the animals. CMV retinitis is the main cause of sight threatening among patients with human immunodeficiency virus (HIV) infection up to 30% prior to highly active antiretroviral therapy (HAART) and reduces to 22% in the HAART era (Pathanapitoon et al., 2013). It typically occurs in immunocompromised HIV-positive patients but incidence among HIV-negative patients has been increasing widely (Iu et al., 2016). Here in we report 8 years review of cytomegalovirus (CMV) retinitis cases from 2011 to 2018 that were referred to our ophthalmology clinic.

Materials and Methods

A retrospective study was conducted to review the clinical profiles and visual outcomes of patients with CMV retinitis treated at Hospital Universiti Sains Malaysia

from January 2011 to June 2018. Demographic data, clinical symptoms and signs, results of investigations and treatment were reviewed from the documented medical records and analysed. CMV retinitis patients with incomplete records or missing data were excluded. This study received approval from hospital director and Human Research Ethics Committee USM (HREC). This study adhered to the guideline of the declaration of Helsinki.

Results and Discussion

This study enrolled 6 patients (7 eyes) that retrospectively reviewed from the documented medical records from January 2011 to December 2018. The demographic data, clinical profiles, investigation results and treatment of the patients were summarised in *Table 1* and *Table 2*. The mean age was 42.5 years ranging from 23 to 74 years. Age less than 50 years old was predominant (4 patients, 66.6%) in this study. There was one patient (case 6) with the age of more than 70 years old. All the patients were Malays

Table 1. *Demographic data, comorbidities and ocular features of CMV retinitis patients.*

Patient	Age/ Gender	Comorbidities	Laterality	Presentation	Ocular features
Case 1	23/ Male	Advance CKD	LE	Reduce vision for 4 months	**LE Panuveitis** Localised corneal ederma Pigmented keratic precipiates Anterior chamber cells 4+ Dense vitritis Retinitis
Case 2	25/ Male	HIV positive	LE	Reduce vision for 1 week	**LE Posterior uveitis** Vitritis 1+ Vasculitis Minimal vitreous haemorrhage
Case 3	42/ Female	DM HTN	RE	Reduce vision for 2 weeks	**RE Panuveitis** Circumcorneal injection Few keratic precipitates Anterior chamber cells 2- 3+ Vitritis 3+ Retinitis Chorioretinal macular scar
Case 4	69/ Female	HTN Thyroid cancer	BE	BE reduce vicion & floaters for 4 days	**RE Posterior uveitis** Vitritis 2+ Vascular sheathing Vasculitis Retinitis **LE Posterior uveitis**
Case 5	46/ Female	No known comorbidity	LE	LE reduce vision & floaters for 3 days	Vitritis 2+ Flame shaped haemorrhage Retinitis **LE Posterior uveitis** Vitritis 2+ Retinitis Multiple choroiditis

Case 6	74/ Male	DM HTN	LE	LE reduce vision & floaters for 2 months	**LE Panuveitis** Pigmented keratic precipitates Anterior chamber cells 1+ Vitritis 2+ Retinitis

**Notes: CKD=Chronic kidney disease, HIV=Human Immunodeficiency virus, DM=Diabetes Mellitus, HTN=Hypertension, IHD=Ischaemic heart disease, RE=right eye, LE=Left eye, BE=Both eye.*

Table 2. *Investigation results, treatment and visual acuity pre and post treatment of CMV retinitis patients.*

Patient	CMV Serology	CD4 (cell/µL)	Infective screening	Treatment	Presenting VA	Final VA
Case 1	CMV IgM negative	510	Positive HSV-1 IgG	Intravitreal ganciclovir (1 injection)	LE PL	LE PL
	CMV IgG positive (titre: 500)	-	-	Oral prednisolone for 4 weeks	-	-
	-	-	-	Gutt prednisolone	-	-
Case 2	CMV IgM negative	70	Positrive HIV	Intravitreal ganiclovir (3 injections)	LE 6/9	LE 6/9
	CMV IgG positive (titre: 286)	-	-	Intravenous ganciclovir for 3 weeks	-	-
	-	-	-	HAART	-	-
Case 3	CMV IgM negative	Not done	Positive HSV-1IgG	Intravenous ganciclovir for 2 weeks	RE CF	RE CF
	CMV IgG positive (titre: 1479)	-	-	-	-	-
Case 4	CMV IgM negative	Not done	Positive HVS-1 IgG	Intravitreal ganciclovir (4 injections)	RE 6/9	RE 6/15
	CMV IgG positive (titre: 141)	-	-	Intravenous ganciclovir for 2 weeks	LE 6/7.5	LE 6/24
Case 5	CMV IgM negative	Not done	Nil	Intravitreal ganciclovir (4 injections)	LE 6/6	LE 6/6
	CMV IgG positive (titre: 218)	-	-	-	-	-
Case 6	CMV IgM negative	Not done	Positive HSV-1 IgG	Oral azithromycin for 6 weeks	LE 6/15	LE 6/6
	CMV IgG positive (titre: 1649)	-	Positive toxoplasma IgG	Intravitreal ganciclovir (6 injections)	-	-
	-	-	-	Gutt prednisolone	-	-

**Notes: CMV=Cytomegalovirus, HSV=Herpes Simplex Virus, HIV=Human Immunodeficiency virus, IgM=Immunoglobulin M, IgG=Immunoglobulin G, CD4=Cluster differentiation 4, HAART=Highly active antiretroviral treatment, VA=Visual acuity, PL=Perception of light, CF=Counting finger, RE=Right eye, LE=Left eye.*

There was equal ratio between male and female. Unilateral manifestation was predominant (5 patients, 83.3%) and only 1 patient (16.7%) with bilateral involvement. Half of the patients have history of hypertension (50.0%). There were 1 patient (16.7%) associated with human immunodeficiency virus (HIV) and 2 patients (33.3%) had diabetes mellitus. None of the patients undergo organ transplant, on corticosteroid usage

or cytotoxic medications. The summary of demographic data and comorbidities is shown in *Table 3*.

Table 3. *Summary of demographic data, laterality and comorbidities of CMV retinitis patients.*

Variables		No of patients (n=6)	Percentage (%)
Ages (year)	Below 30	2	33.3
	30-50	2	33.3
	Above 50	2	33.3
Gender	Male	3	50.0
	Female	3	50.0
Laterality	Unilateral	5	83.3
	Bilateral	1	16.7
Comorbidity	HIV	1	16.7
	DM	2	33.3
	HTN	3	50.0

**Notes: HIV=Human Immunodeficiency virus, DM=Diabetes mellitus, HTN=Hypertension.*

All patients presented with blurring of vision and 3 of them (4 eyes, 57.1%) were associated with floaters. There were 2 eyes (28.6%) presented with visual acuity worse than 6/60 and 5 eyes (71.4%) had vision better than 6/18. Posterior uveitis comprises 57.1% (4 eyes) compared to 42.9% for panuveitis (3 eyes). Patient presented with panuveitis had anterior segment features manifested as circumcorneal injection, corneal oedema, pigmented keratic precipitates and presence of anterior chamber cells. The clinical manifestation of posterior uveitis included vitritis, retinitis with cheese tomato ketchup appearance, vascular sheathing, vasculitis, vitreous haemorrhage, retinal haemorrhage and choroiditis. Vitritis and retinitis were the most common presentation. All of the patients (7 eyes, 100.0%) were found to have mild to dense vitritis and 6 eyes (100.0%) with retinitis. All retinitis lesions were located at zone 1 posterior pole. One patient (case 2) had combination of vitritis, vasculitis and minimal vitreous haemorrhage without retinitis. The summary of clinical profiles of the patients is shown in *Table 4*.

Table 4. *Summary of clinical profiles of 7 eyes with CMV retinitis.*

Clinical features		No of eyes (n=7)	Percentage (%)
Ocular symptoms	Reduce vision	3	42.9
	Reduce vision and floaters	4	57.1
Visual acuity at presentation	Better tahn 6/18	5	71.4
	6/18-6/60	0	0
	Worse than 6/60	2	28.6
Type of intraocular inflammation	Posterior uveitis	4	57.1
	Panuveitis	3	42.9
Anterior segment features	Circumcorneal injection/ Corneal edema	1	14.3
	Pigmented keratic precipitates	3	42.9
	Anterior chamber cells	3	42.9
Posterior segment features	Vitritis	7	100.0
	Retinitis (N=6)	6	100.0
CMV serology (N=6)	**CMV IgM**		

	positive	0	0
	negative	6	100.00
	CMV IgG		
	positive	6	100.00
	negative	0	0
Other positive infective screening (N=6)	HIV	1	16.7
	HSV-1 IgG	4	66.6
	Tocoplasma IgG	1	16.7
CD4 count (cell/µL)(N=2)	0-100	1	50.0
	More than 100	1	50.0
Treatment	Intravitreal ganciclovir	3	42.9
	Intravenous ganciclovir	2	28.5
	Oral prednisolone	1	14.3
	Oral azithromycin	1	14.3
Final visual outcome	Better than 6/18	4	57.1
	6/18-6/60	1	14.3
	Worse than 6/60	2	28.6

**Notes: IgM=Immunoglobulin M, IgG=Immunoglobulin G, CMV=Cytomegalovirus, HIV=Human Immunodeficiency virus, HSV=Herpes Simplex Virus, CD4=Cluster differentiation 4.*

The diagnosis of CMV retinitis was made clinically in all patients and was supported by CMV serology test. All patients showed negative serological CMV IgM but positive CMV serology IgG. There was one patient (case 2) positive for HIV test, three patients had HSV-1 IgG positive (case 1, case 3 and case 4) and one patient had both positive for HSV-1 IgG and serum toxoplasma IgG (case 6). Cluster differentiation 4 (CD4) count was only evaluated in patient with HIV positive (case 2) and young patient (case 1). Patient with HIV positive patient showed low CD4 count (less than 100 cell/uL). Only one patient did not reveal any predisposing medical illness (case 5).

Three patients received intravitreal ganciclovir alone (case 1, case 5 and case 6) while two patients (case 2 and case 4) received combination of intravenous and intravitreal ganciclovir. Only 1 patient (case 3) received intravenous ganciclovir monotherapy. Oral prednisolone was given in one patient (case 1) for dense vitritis at presentation with vision perception of light. One patient (case 6) was also treated with oral azithromycin beside intravitreal ganciclovir in view of positive toxoplasma IgG. HIV positive patient (case 2) was also treated with HAART. The visual acuity showed variable results following treatment. Four eyes had static vision and 1 eye had vision improvement from 6/15 to 6/6. However, 2 eyes had 2 to 5 lines worsening of vision (case 4 with bilateral involvement). Overall, 4 eyes (57.1%) had vision better than 6/18 post treatment (*Table 4*).

CMV retinitis also can be observed among non-HIV patient with immunocompromised status (Shapira et al., 2018; Pathanapitoon et al., 2013). Majority of our patients were immunocompromised. However, only one patient was diagnosed to have HIV. Occurrence of CMV retinitis in immunocompetent usually related to steroid ocular injection or implant (Scoles et al., 2020). None of our patients had steroid ocular injection but older age and limited role of immune dysfunction such as diabetes mellitus, chronic kidney disease and hypertension could be the reason of CMV retinitis (Shapira et al., 2018). The sociodemographic presentation showed that most of our patients are young and less than 50 years old with equal distribution among gender. Out

of six CMV retinitis patients, one patient (16.7%) is HIV positive and another four patients (66.6%) has chronic diseases. This study is consistent with the study done by Shapira et al (Shapira et al., 2018). They reported that CMV retinitis could also occur in HIV seronegative patients. This reflect the underlying HIV epidemic in our settings as mentioned in Malaysia Progress Report on HIV/AIDS 2019 (Suleiman and Chai, 2019) where male and age less than 40 years old are predominantly infected with this immunocompromised disease. Whereas in Northern Thailand, majority female with HIV patients having CMV retinitis (Ausayakhun et al., 2012).

All our patients were clinically diagnosed CMV retinitis with positive CMV IgG. They presented with either posterior uveitis or panuveitis. The classic presentations for CMV retinitis were haemorrhagic retinitis with typical "cottage cheese and ketchup" or "pizza pie" retinopathy, retinal necrosis, variable degree of vitritis and vasculitis with sheathing (Pathanapitoon et al., 2013; Kozak et al., 2013). It is suggested that polymerase chain reaction (PCR) analysis of aqueous or vitreous could yield more specific and sensitive results and confirmed the diagnosis (Shapira et al., 2018). It is done especially in case of diagnostic dilemma when there is absence of identifiable source of immunosuppression (Tran et al., 2003). Site of ocular sampling depends on centre's preference. Anterior chamber paracentesis is less complicated than invasive vitreous tap, but it could yield less viral DNA as compared to vitreous for PCR amplification (Tran et al., 2003).

One of the most common ocular opportunistic infection among HIV positive patients is CMV retinitis and usually occurs in late stage with CD4 count less than 50/µl (Chiotan et al., 2014). We observed that our HIV positive patient presented with minimal vitritis, vasculitis and minimal vitreous haemorrhages with CD4 count of 70 cell/µL. The presentation was posterior uveitis only with very minimal vitritis. In typical HIV patients, the vitreous inflammation is usually mild, and it reflects the presentation of our patient (Schneider et al., 2013). Among HIV-negative patients, all eyes presented with more severe vitritis as compared to the HIV-positive patients. One eye among HIV-negative patients presented with retinitis and vasculitis as well. Wide range of clinical findings has been observed for non-HIV patients with CMV retinitis. As studied by Pathanapitoon et al. (2013) and Schneider et al. (2013), they observed that occlusive vasculitis predominantly affects the arteries and are distant away from area of retinitis among HIV-negative patients with CMV retinitis.

Treatment for CMV retinitis should be individualized. It is based on the severity and location of the retinitis. The retinitis lesion involving zone 1 shall receive both intravitreal and intravenous ganciclovir whereas lesion at the periphery only treated with intravenous ganciclovir alone for 2-3 weeks durations. Level of underlying immune suppression and concomitant medications should also be considered beside the ability to comply with treatment. In general, antiviral therapy is induced at high doses for two to three weeks or until the retinitis stabilizes. All our patients received intravitreal ganciclovir except for one patient who first presented with counting finger vision due to macular scar. Two out of seven eyes had visual acuity worse than 6/60 following treatment. The poor visual outcome in our case review may be due to late presentations (ranging from three days up to four months of symptoms prior treatment) and zone one lesion involvement. According to the Longitudinal Study of Ocular Complications of AIDS (LSOCA) (Jabs et al., 2013), intravitreal ganciclovir therapy alone could lead to poor ocular outcome in terms of retinitis progression, final visual acuity and visual field as compared to intravenous ganciclovir. Medical counterpart

should be involved in the management for the patients as well as the side effects of ganciclovir and patient's systemic condition need to be closely monitored. For HIV patient, although HAART is recommended when CD4 is less than 500 cell/μL but in developing countries, HAART is usually initiated when CD4 was less than 200 cell/μl (Lubis et al., 2014) as in our HIV patient.

Due to emergent of opportunistic infection specifically CMV retinitis which can lead to blindness, patient should be educated and emphasized regarding the symptoms. Patients with chronic diseases and who receive immunomodulators are not exempted to such eye conditions and need to seek medical treatment immediately when develop poor vision. Patients with HIV positive and starting on antiretroviral therapy should also be screened as CMV retinitis has high contribution towards the sight threatening condition as early presentation may halt the progression of the disease.

Conclusion

CMV retinitis was common among young age and immunocompromised status of the patient. Advanced age and chronic medical diseases contribute to the defective cell mediated immunity and should not be overlooked as causes of immunocompromised. Therefore, we should have a high index of suspicious towards the diagnosis of CMV retinitis hence prompt treatment can be initiated. However, visual acuity shows variable outcome following treatment.

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Conflict of interest

The authors have no conflicts of interest to declare.

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