Ocular infection with cytomegalovirus in Thailand: the clinical features, treatments and outcomes

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Purpose: To study the clinical features, treatments and outcomes of ocular cytomegalovirus (CMV) infection.
Methods: Retrospective case series. Medical records of patients who had ocular CMV infection treated at Thammasat university hospital, Thailand from January 2015 to May 2017 were included. Clinical features, treatments and outcomes were analyzed.
Results: Forty-one patients were diagnosed with ocular CMV diseases including infection in immunocompetent patients (n=25, 61%) and infection in immunocompromised cases (n=16, 39%). Among the immunocompetent group, anterior uveitis was the most common manifestation (n=22, 88%). Posner Schlossman syndrome (n=14, 56%) was the majority of CMV anterior uveitis cases. Patients with CMV anterior uveitis had iris atrophy in 90.5% of cases, increased intraocular pressure in 88% of cases, decreased endothelial cell count in 38.1% of cases and coin-shaped lesions in 27.3% of cases. Anti-viral therapy was administered in 88% of cases and 64% of cases needed long-term topical corticosteroids. Most immunocompromised patients were diagnosed with CMV retinitis (93.8%). Almost all patients (n=14, 87.5%) had HIV infection. Immune recovery uveitis developed in 20%. Five cases (31.3%) of CMV retinitis received intravenous ganciclovir with adjunctive intravitreal injections of ganciclovir while 68.8% of cases were treated with only intravitreal injections of ganciclovir. Most patients well responded to treatment with the mortality rate of 6.3%.
Conclusions: Cytomegalovirus can infect both immunocompetent and immunocompromised host with variety of clinical features. Anterior uveitis was common in immunocompetent cases while retinitis was common in immunocompromised patients.
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Introduction

Cytomegalovirus (CMV) is a large-enveloped double-stranded DNA virus in Herpesviridae family, which can be transmitted by saliva, breast milk, sexual contact and organ transplantation.

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Both immunocompetent and immunocompromised host can be infected by CMV in any age group.[1-4]

There are many clinical features caused by this virus which may affect anterior segment, posterior segment or both.[5-7] These diseases vary in severity, from spontaneously resolved to severe visual impairment if the patients were not treated promptly and properly.[8-15]

Our interest was in the variation of clinical features of ocular CMV infection,

therefore the main objective of our study was to report the characteristics of the patients, symptoms, clinical manifestations, treatments and outcomes of this viral infection. From the best of our knowledge, there was no article studying various ocular CMV diseases in both immunocompromised and immunocompetent patients. In this case series, we described these aspects of CMV infected patients treated in Thammasat University Hospital, Thailand.

Methods

We performed a retrospective case review from documented medical records of patients who had ocular CMV infection treated at Thammasat University Hospital from January 2015 to May 2017. Our study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Thammasat University, Pathum Thani, Thailand. Forty-one patients diagnosed with CMV-related diseases were enrolled in this study. Intraocular fluid qualitative polymerase chain reaction (PCR) was performed in all cases of anterior uveitis, intermediate uveitis and acute retinal necrosis and the results yielded CMV. However, CMV retinitis was clinically diagnosed without PCR technique. We excluded the patients who were misdiagnosed with CMV infection but subsequently found to have other specific diseases.

After enrollment, the characteristics of the patients; age, gender, medical illness, immune status, laterality, signs and symptoms, investigations, treatments and outcomes including complications were documented. All data were analyzed using an excel spreadsheet (Excel 2010; Microsoft Corp., Redmond, WA) and reported in term of means, standard deviations and percentages.

Results

Patient characteristics

Forty-one patients diagnosed with ocular CMV diseases were enrolled in this study. We excluded a patient who was initially misdiagnosed with CMV retinitis but subsequently found to have Behcet's disease. There were 25 immunocompetent patients (61%) and 16 immunocompromised patients (39%). The mean age of the patients was 44.9 years (24-67 years in range) and most of them were male (n=32, 78%). In the immunocompromised group, there were 14 human Immunodeficiency virus (HIV)-infected patients (87.5%), 1 systemic lupus erythematosus (SLE) patient (6.3%) and 1 diffuse large B-cell lymphoma patient (6.3%).

Clinical manifestations

The most common presentation was blurred vision (n=24, 58.5%) with various visual acuity. The majority of the patients had best-corrected visual acuity at baseline better than 20/40 (n=29, 70.7%). Other presenting symptoms included eye pain (n=6, 14.6%), red eye (n=1, 2.4%) and floaters (n=1, 2.4%). There were 2 asymptomatic patients (4.9%) and 7 patients (17%) that we could not find records about their presenting symptoms. CMV-related diseases reviewed in our study were unilateral (n=27, 65.9%) rather than bilateral (n=14, 34.1%).

Among the immunocompetent group (n=25), anterior uveitis was the most common manifestation (n=22, 88%), followed by posterior uveitis in 8% (n=2: 1 CMVR, 1 ARN) and intermediate uveitis in 4% (n=1). Posner Schlossman syndrome (PSS, n=14, 56%) made up the majority of CMV anterior uveitis (Table 1). Other clinical manifestations of CMV anterior uveitis included Fuchs heterochromic iridocyclitis (FHI), endotheliitis and combined PSS and endotheliitis. Patients presented with diffused iris atrophy in 90.5%, increased intraocular pressure in 88%, decreased endothelial cell count in 38.1% and coin-shaped lesions in 27.3% of cases.

In this study, almost all CMV retinitis was found in immunocompromised patients (n=15, 93.8%) which all cases were presented with fulminant (classic) form. Almost all immunocompromised patients (n=14, 87.5%) were HIV infection with the mean CD4+ T cell count of 62.7 cells/μL (range 1-163 cells/μL). Nine (64.3%) of

14 HIV-infected patients already received highly active antiretroviral therapy before presentations of ocular diseases. There were 2 patients (14.3%) whom first diagnosed HIV infection from ocular symptoms. Three patients with HIV infection came to eye clinic for screening CMV retinitis prior HAART initiation and they were found to have CMV retinitis. Immune recovery uveitis (IRU) was developed in 3 HIV-infected CMV retinitis patients (20%) which 2 cases presented with unmasking CMV retinitis and 1 case presented with paradoxical worsening of known CMV retinitis.

Treatments and outcomes

In the CMV-related anterior uveitis group, anti-viral therapy was administered in 86.4% of cases (n=19). Three cases were controlled by topical corticosteroids without antiviral therapy (2 PSS, 1 FHI). Antiviral therapy included topical ganciclovir (0.15% ganciclovir gel or 2% ganciclovir solution), valganciclovir, intravenous ganciclovir and intravitreal ganciclovir. All cases used topical corticosteroids for controlling inflammation. The diseases can be controlled by topical corticosterioids without anti-viral therapy in 3 patients (13.6%). Among the patients who received anti-viral therapy in anterior uveitis group (n=19), only 2 patients (10.5%) were able to stop using anti-viral agents and topical cortocosteroids (quiescence period: 2 years and 5.5 years). Five patients (26.3%) had recurrences after cessation of anti-viral agents. Twelve patients (63.2%) never discontinued anti-viral therapy because inflammation occurred after reducing the dose of topical corticosteroids or antiviral therapy. A patient with CMV anterior uveitis received an intravitreal injection of ganciclovir (4 mg/0.04 cc) due to unavailability of topical ganciclovir medication at that point and financial problem for systemic medication. She developed maculopathy (mild scotomas from some areas of macula) after an intravitreal injection. After this case, we stopped treating CMV-related anterior uveitis with intravitreal injections of ganciclovir. A patient presented with CMV intermediate uveitis. Ocular examination showed mild unilateral anterior chamber inflammation, diffuse iris atrophy, vitreous

Table 1: Diagnosis of ocular CMV infection in immunocompetent and immunocompromised patients.

Diagnosis	Immunocompetent patients (n, %)	Immunocompromised patients (n,%)		
		HIV	Non-HIV	Total
Anterior segment disease	22 (88%)	0	0	0
Posner Schlossman syndrome (PSS)	14 (56%)	0	0	0
Fuchs heterochromic iridocyclitis	3 (12%)	0	0	0
Endotheliitis	3 (12%)	0	0	0
Combined PSS with endotheliitis	2 (8%)	0	0	0
Posterior segment disease	3 (12%)	14 (100%)	2 (100%)	16 (100%)
Intermediate uveitis	1 (4%)	0	0	0
CMV retinitis	1 (4%)	14 (87.5%)	1 (SLE,6.3%)	15 (93.8%)
Acute retinal necrosis	1 (4%)	0	1 (DLBCL,6.3%)	1 (6.3%)
All	25 (61%)	14	2	16 (39%)

SLE: Systemic lupus erythematosus, CMV: cytomegalovirus, DLBCL: diffuse large B-cell lymphoma

haze and normal retina. Both aqueous and vitreous PCR yielded CMV. He was treated with therapeutic vitrectomy and topical corticosteroids. Inflammation was controlled after treatment without antiviral therapy.

CMV retinitis (n=16) has been found in 14 patients with HIV infection, 1 patient with SLE and 1 immunocompetent patient. Five cases (31.3%) of CMV retinitis received combined intravenous ganciclovir and intravitreal injections of ganciclovir while other 11 cases (68.8%) were treated with only intravitreal injections of ganciclovir. Most patients (n=15, 93.8%) responded well to treatment. The mortality rate of patients with CMV infection in acquire immune deficiency syndrome was 6.3%. CMV related acute retinal necrosis patients was found in 2 cases (1 immunocompetent case, 1 diffuse B cell lymphoma), treated with intravenous ganciclovir injections adjunctive with intravitreal injections of ganciclovir and followed by valganciclovir therapy.

In the immunocompetent group, complications included ocular hypertension in 40% of cases (n=10), glaucoma in 48% of cases (n=12), cataract in 56% of cases (n=14), endothelial cell count loss in 40% of cases (n=10), corneal decompensation in 8% of cases (n=2) and epiretinal membrane in 20% of cases (n=5). No cystoid macular edema was found. Surgical management included cataract surgery in 32% of cases (n=8), glaucoma surgery in 44% of cases (n=11) and keratoplasty in 8% of cases (n=2).

In the immunocompromised group, complications included ocular hypertension in 25% of cases (n=16), cataract in 25% of cases (n=4), rhegmatogenous retinal detachment in 31.3% of cases (n=5) and cystoid macular edema in 6.3% of cases (n=1). No glaucoma was developed. Cataract surgery was performed in 12.5% of cases (n=2).

In both groups, 18 patients received systemic antiviral agents and 16.7% of cases (n=3) developed bone marrow suppression. Onset of bone marrow suppression of 3 cases was 4 weeks, 6 weeks and 30 weeks after valganciclovir initiation.

Discussion

In our study, clinical features of CMV-related ocular diseases were varied with anterior uveitis mostly presented in immunocompetent host and posterior uveitis frequently occurred in immunocompromised host. We do not know the reason why the target site of the virus differed among hosts with various immune statuses.

Regarding CMV related anterior uveitis, there were various clinical presentations, including PSS, FHI, endotheliitis, and combined presentation such as PSS with endotheliitis.[16-22] We hypothesized that the amount of virus in the innoculation site may be the factor to determine the clinical presentation. In PSS, virus may be mostly located in trabecular meshwork. This may be different from FHI which infected site mostly located in iris. Corneal endothelium may be the target site for corneal endotheliitis.[18] From our study, the clinical clues suggesting CMV related anterior uveitis included diffused iris atrophy (most frequent finding) followed by increased intraocular pressure. Additional suggestive signs included coin-shaped lesions, decreased endothelial cell count.[21] Glaucoma was a common complication. Most patients (88%) had increased intraocular pressure with 48% progressed to glaucoma and 44% needed glaucoma surgery to control their intraocular pressure. PSS was the most common clinical presentation in CMV related anterior uveitis. In the past, PSS was considered to be a benign condition.[17] In our study, glaucoma can develop in nearly half of patients. We would like to emphasize that PSS is not always benign. Glaucoma monitoring is essential and the patient can develop blindness in this disease.

In this study, immune recovery uveitis was found in 20% of HIV patients. This is in range of previous records, which are varied between studies, ranging from 1.5-63.3%.[23, 24] This may be because of there is no specific criteria for diagnosis IRU and depend on awareness of the ophthalmologists. The risk of IRU included low CD4+ T cell count and large infected areas of CMV retinitis. The high incidence may be from large area

Table 2: Complications of ocular CMV infection in immunocompetent and immunocompromised patients.

Complications	n	Increased IOP		Need glaucoma surgery	Cataract	Cataract surgery	EDC loss (eyes)	Corneal decompensation	keratoplasty	CME	RRD	ERM	Maculopathy	Optic atrophy	Immune recovery uveitis
		OHT	Glaucoma												
Immunocompetent host															
PSS	14	8	6	10[a]	9	4	4	0	0	0	0	1	1[c]	0	0
FHI	3	1	1	0	0	0	2	0	0	0	0	2	0	0	0
Endotheliitis	2	1	1	0	2	2	3	0	0	0	0	1	0	0	0
Bullous keratopathy	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0
Combined PSS with endotheliitis	2	0	2	1[b]	1	0	1	1	1	0	0	0	0	0	0
Intermediate uveitis	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CMV retinitis	1	0	1	0	1	1	0	0	0	0	0	1	0	0	0
Acute retinal necrosis	1	0	0	0	1	1	0	0	0	0	1	0	0	1	0
Total	25	10 (40%)	12 (48%)	11 (44%)	14 (56%)	8 (32%)	10 (40%)	2 (8%)	2 (8%)	0	1 (4%)	5 (20%)	1 (4%)	1 (4%)	0
Immunocompromised host															
CMV retinitis	15	1	0	0	2	2	-	0	0	1	5	1	1	5	3 (20%)
Acute retinal necrosis	1	1	0	0	0	0	-	0	0	0	0	0	0	0	0
Total	16	2 (12.5%)	0	0	2 (12.5%)	2 (12.5%)	-	0	0	1 (6.3%)	5 (31.3%)	1 (6.3%)	1 (6.3%)	5 (31.3%)	3

IOP: intraocular pressure, OHT: ocular hypertension, CME: cystoid macular edema, RRD: rhegmatogenous retinal detachment, ERM: epiretinal membrane, PSS: Posner Schlossman syndrome, FHI: Fuchs heterochromic iridocyclitis

Corneal endothelial cell density loss (EDC loss) >20% in unilateral case compare with fellow eye or loss >20% compare with lower margin of normal range of each age group in bilateral cases.

a: Trabeculectomy with mitomycin C 8 patients, combined phacoemulsificatoin with intraocular lens implantation with trabeculectomy with mitomycin C 2 patients

b: Trabeculectomy with mitomycin C

c: Toxic from intravitreal ganciclovir injection

of retinitis and high number of patients who had low CD4+ T cell count. We also believe that the practitioner's awareness is another factor involving the incidence of immune recovery uveitis because IRU can present with mild or severe inflammation. Signs of immune recovery uveitis included iritis, mild to severe vitritis, macular edema, epiretinal membrane formation, neovascularization of the retina or optic disc and papillitis.[24]

CMV-related ocular diseases vary in severity, from spontaneously resolved to severe visual impairment and many complications can occur both from the diseases themselves and from the treatments.[25, 26] The complications found in our study are ocular hypertension, glaucoma, cataract, endothelial cell loss, corneal decompensation, cystoid macular edema, retinal detachment, epiretinal membrane, maculopathy and optic neuropathy. Leukopenia from systemic anti-CMV medication can occur in weeks or years. Blood monitoring is essential during systemic therapy.

The important limitations of our study are the incomplete information in the medical records and small number of patients included in the study.

Conclusion

Cytomegalovirus can infect both immunocompetent and immunocompromised host with variety of clinical features. Anterior uveitis was common in immunocompetent cases while retinitis was common in immunocompromised patients.

References

1.Ausayakhun S, Keenan JD, Ausayakhun S, Jirawison C, Khouri CM, Skalet AH, et al. Clinical features of newly diagnosed cytomegalovirus retinitis in northern Thailand. Am J Ophthalmol. 2012;153(5):923-31 e1.

2.Pathanapitoon K, Tesavibul N, Choopong P, Boonsopon S, Kongyai N, Ausayakhun S, et al. Clinical manifestations of cytomegalovirus-associated posterior uveitis and panuveitis in patients without human immunodeficiency virus infection. JAMA Ophthalmol. 2013;131(5):638-45.

3.Colby DJ, Vo DQ, Teoh SC, Tam NT, Liem NT, Lu D, et al. Prevalence and predictors of cytomegalovirus retinitis in HIV-infected patients with low CD4 lymphocyte counts in Vietnam. Int J STD AIDS. 2014;25(7):516-22.

4.Huang G, Jiang Q, Li M, Lu Y, Wang Z. Retrospective study of cytomegalovirus retinitis complicated with acquired immunodeficiency syndrome. Int J Clin Exp Med. 2015;8(6):9537-42.

5.Kongyai N, Sirirungsi W, Pathanapitoon K, Tananuvat N, Kunavisarut P, Leechanachai P, et al. Viral causes of unexplained anterior uveitis in Thailand. Eye (Lond). 2012;26(4):529-34.

6.Kongyai N, Pathanapitoon K, Sirirungsi W, Kunavisarut P, de Groot-Mijnes JD, Rothova A. Infectious causes of posterior uveitis and panuveitis in Thailand. Jpn J Ophthalmol. 2012;56(4):390-5.

7.Yoshida A, Obata H, Kawashima H. Cytomegalovirus Uveitis with Hypopyon Mimicking Bacterial Endophthalmitis. Case Rep Ophthalmol Med. 2015;2015:489813.

8.Pathanapitoon K, Ausayakhun S, Kunavisarut P, Wattananikorn S, Ausayakhun S, Leeungurastien T, et al. Blindness and low vision in a tertiary ophthalmologic center in Thailand: the importance of cytomegalovirus retinitis. Retina. 2007;27(5):635-40.

9.Shi Y, Lu H, He T, Yang Y, Liu L, Zhang R, et al. Prevalence and clinical management of cytomegalovirus retinitis in AIDS patients in Shanghai, China. BMC Infect Dis. 2011;11:326.

10.Leenasirimakul P, Liu Y, Jirawison C, Khienprasit N, Kamphaengkham S, Ausayakhun S, et al. Risk factors for CMV retinitis among individuals with HIV and low CD4 count in northern Thailand: importance of access to healthcare. Br J Ophthalmol. 2016;100(8):1017-21.

11.Ford N, Shubber Z, Saranchuk P, Pathai

S, Durier N, O'Brien DP, et al. Burden of HIV-related cytomegalovirus retinitis in resource-limited settings: a systematic review. Clin Infect Dis. 2013;57(9):1351-61.
12.Lamichhane G, Shah DN, Sharma S, Chaudhary M. Ocular manifestations in HIV/AIDS cases in Nepal. Nepal J Ophthalmol. 2010;2(1):45-50.
13.Liu Y, Chen AS, Kamphaengkham S, Leenasirimakul P, Jirawison C, Ausayakhun S, et al. Diagnostic Utility of Ocular Symptoms and Vision for Cytomegalovirus Retinitis. PLoS One. 2016;11(10):e0165564.
14.Heiden D, Ford N, Wilson D, Rodriguez WR, Margolis T, Janssens B, et al. Cytomegalovirus retinitis: the neglected disease of the AIDS pandemic. PLoS Med. 2007;4(12):e334.
15.Heiden D, Saranchuk P. CMV retinitis in China and SE Asia: the way forward. BMC Infect Dis. 2011;11:327.
16.Takase H, Kubono R, Terada Y, Imai A, Fukuda S, Tomita M, et al. Comparison of the ocular characteristics of anterior uveitis caused by herpes simplex virus, varicella-zoster virus, and cytomegalovirus. Jpn J Ophthalmol. 2014;58(6):473-82.
17.Chee SP, Bacsal K, Jap A, Se-Thoe SY, Cheng CL, Tan BH. Clinical features of cytomegalovirus anterior uveitis in immunocompetent patients. Am J Ophthalmol. 2008;145(5):834-40.
18.Alfawaz A. Cytomegalovirus-related corneal endotheliitis: A review article. Saudi J Ophthalmol. 2013;27(1):47-9.
19.Woo JH, Lim WK, Ho SL, Teoh SC. Characteristics of Cytomegalovirus Uveitis in Immunocompetent Patients. Ocul Immunol Inflamm. 2015;23(5):378-83.
20.Chee SP, Jap A. Presumed fuchs heterochromic iridocyclitis and Posner-Schlossman syndrome: comparison of cytomegalovirus-positive and negative eyes. Am J Ophthalmol. 2008;146(6):883-9 e1.
21.Koizumi N, Inatomi T, Suzuki T, Shiraishi A, Ohashi Y, Kandori M, et al. Clinical features and management of cytomegalovirus corneal endotheliitis: analysis of 106 cases from the Japan corneal endotheliitis study. Br J Ophthalmol. 2015;99(1):54-8.
22.Chee SP, Jap A. Cytomegalovirus anterior uveitis: outcome of treatment. Br J Ophthalmol. 2010;94(12):1648-52.
23.Kempen JH, Min YI, Freeman WR, Holland GN, Friedberg DN, Dieterich DT, et al. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. Ophthalmology. 2006;113(4):684-94.
24.Urban B, Bakunowicz-Lazarczyk A, Michalczuk M. Immune recovery uveitis: pathogenesis, clinical symptoms, and treatment. Mediators Inflamm. 2014;2014:971417.
25.Accorinti M, Gilardi M, Pirraglia MP, Amorelli GM, Nardella C, Abicca I, et al. Cytomegalovirus anterior uveitis: long-term follow-up of immunocompetent patients. Graefes Arch Clin Exp Ophthalmol. 2014;252(11):1817-24.
26.M, Chen J, Ausayakhun S, Kunavisarut P, Vichitvejpaisal P, Ausayakhun S, et al. Retinal detachment associated with AIDS-related cytomegalovirus retinitis: risk factors in a resource-limited setting. Am J Ophthalmol. 2015;159(1):185-92.