

Cytomegalovirus retinitis in non-HIV patients in Chiang Mai University Hospital

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Objective To study the associated factor of cytomegalovirus (CMV) retinitis in patients without human immunodeficiency virus (HIV) infection.

Design Retrospective case series.

Methods A retrospective review of medical records from 12 eyes of 9 consecutive patients with cytomegalovirus retinitis in the absence of HIV infection was conducted at Chiang Mai University Hospital from January 2006 to August 2012. Demographic data, underlying disease and other medical conditions, previous treatment for underlying disease, clinical manifestation and treatment for CMV retinitis were recorded and analyzed for associating factors that increase the risk of CMV retinitis.

Results The average age of patients was 53.9 years (SD= 10.26, range 35-65 years). Three patients (33.33%) had bilateral CMV retinitis. The underlying diseases of the patients included systemic lupus erythematosus (n=2, 22.22%), renal insufficiency (n=5, 55.56%), polymyositis (n=1, 11.11%), myasthenia gravis (n=1, 11.11%), cell-mediated immunity (CMI) defect (n=1, 11.11%) and metabolic diseases (n=5, 55.56%). Two patients (22.22%) had renal transplantation, while 8 (88.89%) received immunosuppressive drugs. Two patients (22.22%) had CMV nephropathy and CMV colitis. All of the patients had initial manifestation with visual impairment.

Conclusions In the case series of this study, CMV retinitis was observed mostly in patients receiving therapy with an immunosuppressive agent. It was suggested that patients should receive frequent and careful ophthalmic examination of CMV retinitis after initiation of immunosuppressive therapy, and symptomatic patients with clinical signs such as visual impairment should be assessed, as they can indicate manifestations of CMV retinitis. **Chiang Mai Medical Journal 2013;52(3-4):65-72.**

Keywords : cytomegalovirus retinitis, non-HIV

Introduction

Cytomegalovirus (CMV) retinitis classically occurs in advanced human immunodeficiency virus (HIV) infection, when CD4+ T-cell counts are less than 50 cells per μL [1-5]. CMV retinitis

is the most opportunistic ocular infection and also the main cause of blindness in HIV infected patients in Thailand [4,5]. The prevalence of CMV retinitis in the era of highly active antiretroviral therapy (HAART) is approximately 25-40% [4,5], but is rare in forms of immunocompetent patients [6-8]. However, there have been some case reports and case series of CMV retinitis in non HIV-infected patients, such as those who received subtenon triamcinolone acetonide [9] or intravitreal triamcinolone acetonide [10-13] and organ transplants [6,14-20]; those undergoing long-term immunosuppressive medication [6], and those who have systemic lupus erythematosus [21-22], leukemia [23-25] and lymphoma [26].

The main objective of this study was to identify associated factors that increase the risk of CMV retinitis in non-HIV patients. Hopefully, the results of this study may help in consideration for screening, and provide early treatment for the prevention of visual impairment and blindness.

Methods

This retrospective study identified and reviewed the medical records of consecutive HIV-negative patients diagnosed with CMV retinitis at the CMV Retinitis Clinic, Chiang Mai University Hospital, Chiang Mai, Thailand, from January 1, 2006 to August 31, 2012. Collected data included age, sex, visual acuity, underlying diseases, other surgical conditions, previous treatment for underlying diseases (with particular emphasis on immunosuppressant medication), clinical manifestation and treatment for CMV retinitis. Data were described in these patients for associated factors of CMV retinitis. Ethical approval was obtained from the Research Ethics Committee at Chiang Mai University (No. 101/2011). This study had no conflict of interest.

Results

Twelve eyes of 9 patients met the study criteria. The average age of the patients was 53.9 years (SD = 10.26), with 5 (55.56%) being male

and 4 (44.44%) female. Bilateral CMV retinitis was present in 3 patients (33.33%). Their underlying diseases included systemic lupus erythematosus in 2 patients (22.22%), renal insufficiency in 5 (55.56%), polymyositis in 1 patient (11.11%), myasthenia gravis in 1 (11.11%), cell-mediated immunity (CMI) defect in 1 (11.11%), and metabolic diseases (diabetes mellitus, hypertension and hyperlipidemia) in five patients (55.56%). Two patients (22.22%) had renal transplantation and 8 received immunosuppressive drugs (88.89%). There were other systemic cytomegalovirus infections (CMV nephropathy and CMV colitis) in 2 patients (22.22%) (Table 1).

All patients had initial manifestation of CMV with visual impairment ranging from a period of 2 weeks to 3 months. Of 12 eyes with CMV retinitis, 8 (66.67%) had lesions in zone 2 that did not involve the fovea, and 2 (16.67%) had lesions in both zone 1 and 2. The final visual acuity measurement was worse than 6/18, but equal to or better and worse than 6/60 in 4 of 12 eyes (33.33%) and 4 of 12 eyes (33.33%), respectively (Table 2).

In case number 2 of the 9 in this series, a 40-year-old woman visited the CMV Retinitis Clinic with 1 month's symptoms of blurred vision and floaters of the left eye. Her right eye had been blind from unknown causes since she was young. Her medical history was SLE and nephrotic syndrome diagnosed at a private hospital 3 years previously. She had received endoxan at 50 mg and prednisolone at 10 mg daily for 3 years.

The best-corrected visual acuity was no perception to light in the right eye and 6/36 in the left one, with intraocular pressure of 4 mmHg and 12 mmHg in the right and left eye, respectively. Slit lamp biomicroscopy showed fine keratic precipitates, 1+ aqueous cells and 1.5+ vitreous inflammatory cells in the left eye. Fundoscopic examination revealed an area of retinitis and retinal hemorrhage in zone 1 and 2 (Figure 1A and 1B).

Pertinent laboratory findings included the following; human immunodeficiency virus antibody was negative, aqueous fluid analysis by polymerase chain reaction (PCR) detected CMV,

Table 1. Demographic data of patients with CMV retinitis without HIV infected

No	Age	Sex	Diagnosis	Treatment of CMVR(Eye)	Associated eye disease / Eye surgery	Underlying disease/Other diseases	Surgery	Treatment (immunosuppressive)
1	62	Male	CMVR, OU	Not available	Secondary glaucoma (uveitic glaucoma), OU / Trabeculectomy, OD	Hyperlipidemia	Cadaveric kidney transplantations	Everolimus
2	40	Female	CMVR, OS	IVT Gancyclovir IV Gancyclovir	Retinal break, OD	Systemic lupus erythematosus Nephrotic syndrome	-	Prednisolone Cyclophosphamide
3	35	Female	CMVR, OU Mild anterior uveitis, OU	IVT Gancyclovir OU	-	Systemic lupus erythematosus Nephrotic syndrome Hypertension, Hyperlipidemia Disseminated herpes infection Fungal skin infection	-	Prednisolone Cyclophosphamide Cyclosporin A
4	57	Male	CMVR, OS	IV Gancyclovir	Tractional retinal detachment OS	Diabetic nephropathy End stage renal disease Diabetes mellitus Hypertension CMV nephropathy	Kidney transplant with chronic graft rejection	Everolimus Tracolimus Cyclosporin A Bortezomib Methylprednisolone Prednisolone
5	50	Male	CMVR, OU	IVT Gancyclovir, - OU	-	T cell Non-hodgkin lymphoma	-	Chemotherapy x 2 cycles
6	60	Female	CMVR, OD	IVT Gancyclovir, - OD	-	Myasthenia gravis Hypertension	Thymectomy	Azathioprine
7	65	Female	CMVR, OS	IVT Gancyclovir, OS	Herpes zoster ophthalmicus	Cell-mediated immunity defect Myelodysplastic syndrome with anemia	-	-
8	56	Male	CMVR, OS	IV Gancyclovir OS, Valganciclovir, oral	-	Polymyositis	-	Azathioprine Methotrexate Prednisolone
9	60	Male	CMVR, OS	IV T Gancyclovir OS	Mild NPDR OU	Diabetic nephropathy with Diabetic neuropathy Membranoproliferative glomerulonephritis Hypertension, Hyperlipidemia Double vessel disease CMV colitis	-	Mycophenolate mofetil (MMF)

CMV = Cytomegalovirus, CMVR = Cytomegalovirus retinitis, OU = Both eyes, OD = Right eye, OS = Left eye, IVT = Intravitreal injection, IV = Intravenous, NPDR = Non proliferative diabetic retinopathy

Table 2. Clinical characteristics of patients with CMV retinitis without HIV infected

No.	Diagnosis	BCVA initial	BCVA last	Presenting symptoms	Duration	Zone	Lesion	Note
1	CMVR, OU	OD 6/6 OS 6/36	OD 6/6 OS 6/60	Blurred vision, OD	1 month	Zone 2	Scar	
2	CMVR, OS	OD No PL OS 6/36	OD No PL OS HM	Blurred vision, OS	1 month	Zone 1&2	Retinal hemorrhage, exudates and vitreous cell 1.5+	Aqueous PCR positive for CMV
3	CMVR, OU Mild anterior uveitis, OU	OD 6/12 OS 6/36	OD 6/12 OS 6/24	Blurred vision, OU	1 month	Zone 2	Retinal hemorrhage, exudates and vascular sheathing	
4	CMVR, OS	OD 6/60 OS 1/60	OD 6/6 OS FC	Blurred vision + floater, OS	2 weeks	Zone 1&2	Retinal hemorrhage, exudates, vascular sheathing, cotton wool spots, retinal ischemia and vitreous cell	
5	CMVR, OU	OD 6/12 OS 6/9	OD FC OS 6/24	Blurred vision, OS	2 weeks	Zone 2	Focal retinitis, frosted branch angitis, vascular sheathing and vitreous cell 1+	Aqueous PCR positive for CMV
6	CMVR, OD	OD 6/9 OS 6/12	OD 6/6 OS 6/6	Blurred vision, OD	1 month	Zone 2	Retinal hemorrhage, white retinal infiltrate and vitreous cell 2 +	
7	CMVR, OS	OD FC OS 6/24	OD HM OS 2/60	Blurred vision, OS	2 months	Zone 2	Retinal hemorrhage, exudates, vascular sheathing, retinitis and vitreous cell 1+	CD4 count 483 cell/mm ³ , 24%
8	CMVR, OS	OD 6/6 OS 6/6	OD 6/6 OS 6/12	Blurred vision, OS	1 month	Zone 2	Retinal hemorrhage, exudates and retinal necrosis	
9	CMVR, OS	OD 6/12 OS 6/36	OD 6/18 OS 6/24	Blurred vision, OS	3 months	Zone 2	Retinal hemorrhage, exudates and vascular sheathing	

CMV = cytomegalovirus, CMVR = cytomegalovirus retinitis, OU = both eyes, OD = right eye, OS = left eye, OS = left eye, OD = right eye, PCR = polymerase chain reaction

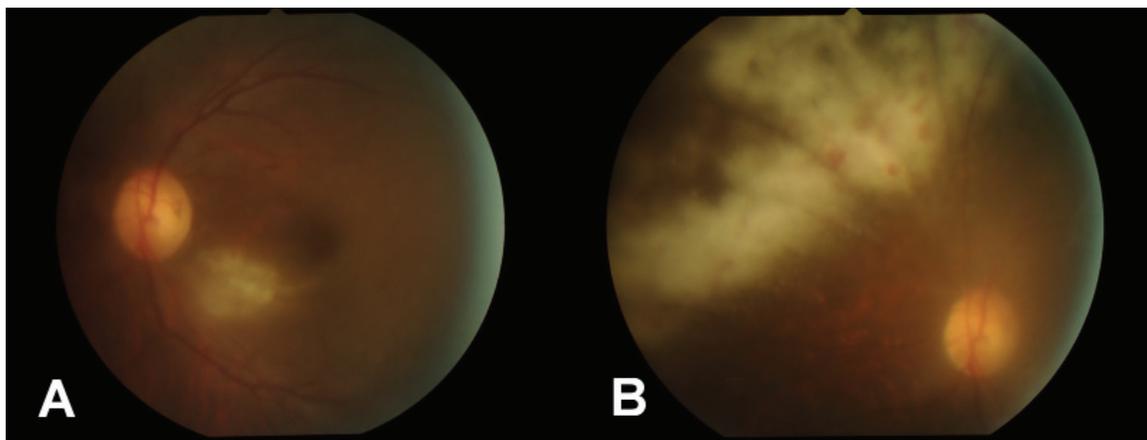


Figure 1. A, Fundus photography of the left eye showing an area of retinitis in zone 1; B, retinitis and retinal hemorrhage in zone 2.

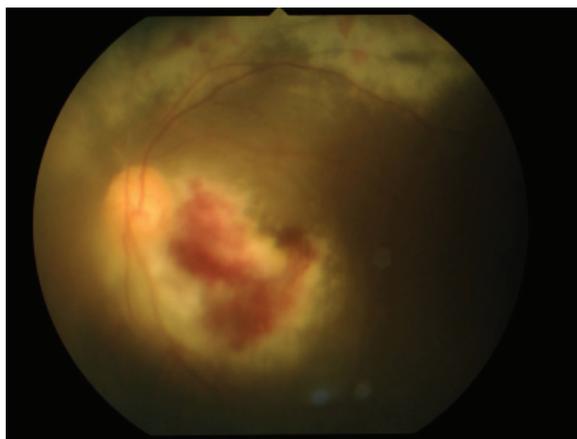


Figure 2. Lesion progression in the fourth week of therapy.

but no herpes simplex virus, varicella zoster virus or toxoplasmosis was found.

Given the probable relationship between the patient's medication and development of CMV retinitis, the endoxan was discontinued and prednisolone dose reduced to 5 mg/day. The patient was treated with intravitreal gancyclovir injections (2 mg/0.05 mL) once a week for 3 weeks as induction therapy. Repeated fundoscopic examination at week 4 of the therapy showed progression of the lesions (Figure 2). The treatment was shifted to intravenous gancyclovir (125 mg every 12 hr) for 2 weeks, followed by intravitreal maintenance therapy, with gancyclovir injections (2 mg/0.05 mL) for 2 visits in

every 2 weeks, then 2 visits in every 3 weeks. Fundoscopic examination showed regression of the lesions 3 months after initial therapy.

In case number 5 of the 9 in this series, a 50-year-old man was referred to the CMV Retinitis Clinic with 2 week's symptoms of blurred vision in the left eye, and he was suspected of having CMV retinitis with differential diagnosis of intraocular lymphoma. An ocular examination at a provincial hospital showed 1+ aqueous cells in both eyes, and bilateral disc edema and 4+ anterior vitreous cells in the left eye. Investigations at that hospital yielded the following findings: human immunodeficiency virus antibody was negative, VDRL and TPHA were non reactive and a CT brain scan had no evidence of increased intracranial pressure. The patient had a remarkable history of T-cell non Hodgkin lymphoma, diagnosed 2 years previously. He received 2 cycles of chemotherapy (name of drug not documented).

The patient was seen at the CMV Retinitis Clinic for evaluation. His best-corrected visual acuity was 6/12 and 6/9 in the right and left eye, respectively, with intraocular pressure of 10 mmHg and 12 mmHg in the right and left eye, respectively. Slit lamp biomicroscopy showed fine keratic precipitates in the left eye, no aqueous cells in the right eye, 2+ aqueous cells in the left eye and 1+ vitreous inflammatory cells in the left eye. Fundoscopic examination revealed

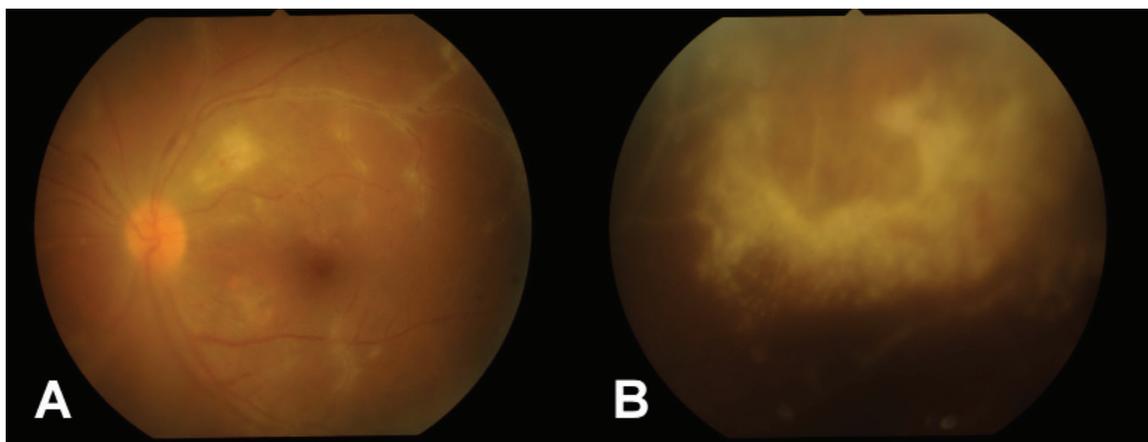


Figure 3. A, Fundus photography of the left eye showing an area of focal retinitis in zone 2; B, perivascular sheathing.

epi-macular membrane at the macula in the right eye, an area of focal retinitis in zone 2 and perivascular sheathing in the left eye (Figure 3A and 3B).

Pertinent laboratory findings included the following: aqueous fluid analysis by PCR detected CMV, but not herpes simplex virus, varicella zoster virus or toxoplasmosis. Toxoplasma IgG titer was reactive (87.5 IU/mL), Toxoplasma IgM titer non reactive, white blood cell count was 22,980 cells per cu.mm., lymphocyte 19.9%, hematocrit 33.8%, hemoglobin 11.0 g/dL, and platelet count 38,000 cells per cu.mm.

The patient was treated with induction therapy of intravitreal gancyclovir injections (2 mg/0.05 mL) once a week for 6 weeks, then maintenance therapy with 2 mg of intravitreal gancyclovir injections for 2 visits in every 2 weeks, then 2 visits in every 3 weeks. The lesion became regressive at 5 weeks after initial therapy and turned to a scar at week [8].

Discussion

CMV retinitis is likely seen to have higher frequency in patients on immunosuppressive therapy and those who had underlying disease with renal problems. More than half of the patients in this study had moderate visual impairment or worse (VA < 6/18) in their final visit. The initial manifestation of all patients was

visual impairment. A variable period of time had passed before patients sought ophthalmic treatment, which may have been due to the mild degree of visual symptoms and slow progression of the disease, or the CMV lesion not involving the fovea (zone 1).

The results of this study are similar to those from cases reported previously [17,20-25], in which CMV retinitis may have occurred after a patient had received immunosuppressive therapy for preventing organ rejection after transplantation, or for treatment of systemic disease.

The incidence rate of CMV retinitis in individuals with AIDS was higher than that in those with a CD4+ T cell count of normally below 50 cells/ μ L[3] prior to treatment. Nevertheless, there was no relationship with non-HIV CMV retinitis patients in this study. CD4 blood test data were recorded in only 1 patient, who was diagnosed with cell-mediated immunity (CMI) defect and received no immunosuppressive treatment or steroids, and had a CD4 count of 483 cell/ μ L. Wagle *et al* [15] also reported a different immunological profile in a transplant recipient with CMV retinitis by specifying a CD4 cell count of 711 cell/ μ L.

The limitations of this study were due to availability and cost of the PCR examination, which diagnosed patients with CMV retinitis by clinical manifestation, and this was confirmed by

the PCR method in some patients. Nevertheless, this fundoscopic approach has demonstrated high accuracy in diagnosing CMV retinitis [6].

This study recommended that patients receive a careful ophthalmic examination for CMV retinitis (including that for end-organ manifestations of CMV infection; such as pneumonitis, hepatitis, colitis and nephritis) frequently after initiation of immunosuppressive therapy. Also, symptomatic patients with clinical signs such as visual impairment, cough and dyspnea, or diarrhea, which can indicate end-organ manifestations of CMV infection, should be assessed.

Conclusion

From the prevalence of CMV retinitis in this case series, CMV retinitis and other CMV infections were observed in patients receiving therapy with immunosuppressive agents. CMV retinitis should be considered in immunosuppressed patients, and earlier screening and treatment of CMV retinitis may limit progression of the disease and might prevent visual impairment [17,27].

Acknowledgements

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Conflicts of interest

This study has no conflict of interest.

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จอประสาทตาอักเสบไซโตเมกกาโลไวรัสในผู้ป่วยที่ไม่ได้ติดเชื้อเอชไอวี ในโรงพยาบาลมหาวิทยาลัยราชภัฏ

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ภาควิชาจักษุวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

วัตถุประสงค์ เพื่อศึกษาปัจจัยที่มีผลเกี่ยวข้อง (associated factors) กับโรคจอประสาทตาอักเสบจากไซโตเมกกาโลไวรัส (CMV retinitis) ในผู้ป่วยที่ไม่ได้ติดเชื้อไวรัสเอชไอวี ในโรงพยาบาลมหาวิทยาลัยราชภัฏเชียงใหม่

วิธีการศึกษา การศึกษาย้อนหลังของผู้ป่วย 9 ราย 12 ตา ที่เป็นโรคจอประสาทตาอักเสบจากไซโตเมกกาโลไวรัส ที่มีผลตรวจเลือดภูมิคุ้มกันบกพร่อง เอชไอวี เป็นผลลบ ในโรงพยาบาลมหาวิทยาลัยราชภัฏเชียงใหม่ ระหว่าง 1 มกราคม 2549 ถึง 31 สิงหาคม 2555 โดยการทบทวนเวชระเบียน นำข้อมูลทั่วไป เพศ อายุ โรคประจำตัว ลักษณะการแสดงของโรค วิธีการรักษา และระดับการมองเห็นหลังการรักษา มาวิเคราะห์หาปัจจัยร่วมที่เกี่ยวข้องกับการเกิดโรค

ผลการศึกษา อายุเฉลี่ยของผู้ป่วยเท่ากับ 53.9 ปี (SD = 10.26 ปี ช่วงอายุ 35 ถึง 65 ปี) เป็นผู้ป่วยเพศชาย 5 ราย (ร้อยละ 55.56) เพศหญิง 4 ราย (ร้อยละ 44.44) ผู้ป่วย 3 ราย (ร้อยละ 33.33) เป็น CMV retinitis ทั้งสองตา พบโรคประจำตัวของผู้ป่วย ได้แก่ systemic lupus erythematosus 2 ราย (ร้อยละ 22.22) โรคไต 5 ราย (ร้อยละ 55.56) polymyositis 1 ราย (ร้อยละ 11.11) myasthenia gravis 1 ราย (ร้อยละ 11.11) cell-mediated immunity (CMI) defect 1 ราย (ร้อยละ 11.11) และโรคทางเมตาบอลิซึม (diabetes mellitus, hypertension and hyperlipidemia) 5 ราย (ร้อยละ 55.56) ผู้ป่วย 2 ราย (ร้อยละ 22.22) ได้รับการเปลี่ยนถ่ายไต และผู้ป่วย 8 รายได้รับการควบคุมภูมิคุ้มกัน (ร้อยละ 88.89) ผู้ป่วย 2 รายมีการติดเชื้อ CMV ที่อวัยวะอื่น ได้แก่ ไตและลำไส้ (CMV nephropathy and CMV colitis) ผู้ป่วยทั้งหมดมีอาการนำคืออาการตามัว

สรุปผลการศึกษา ผู้ป่วยส่วนใหญ่ในการศึกษามีปัจจัยร่วมคือการได้รับยากดภูมิคุ้มกัน จึงแนะนำว่าผู้ป่วยควรได้รับการตรวจตาอย่างละเอียดและสม่ำเสมอหลังการได้รับยากดภูมิคุ้มกัน และได้รับการตรวจตามเมื่อมีอาการตามัวซึ่งเป็นอาการบ่งชี้ถึงภาวะจอประสาทตาอักเสบไซโตเมกกาโลไวรัสในผู้ป่วยกลุ่มนี้ *เชียงใหม่เวชสาร* 2556;52(3-4):65-72.

คำสำคัญ: จอประสาทตาอักเสบไซโตเมกกาโลไวรัส ไม่ได้ติดเชื้อ เอชไอวี โรงพยาบาลมหาวิทยาลัยราชภัฏเชียงใหม่