Published in final edited form as:

Am J Ophthalmol. 2012 May ; 153(5): 923–931.e1. doi:10.1016/j.ajo.2011.10.012.

Clinical Features of Newly Diagnosed Cytomegalovirus Retinitis in Northern Thailand

Somsanguan Ausayakhun^{1,*}, Jeremy D Keenan^{2,3,*}, Sakarin Ausayakhun¹, Choeng Jirawison¹, Claire M Khouri², Alison H Skalet^{2,3}, David Heiden⁴, Gary N Holland⁵, and Todd P Margolis^{2,3}

¹ Department of Ophthalmology, Faculty of Medicine, Chiang Mai University, Thailand ² Francis I. Proctor Foundation, University of California, San Francisco, USA ³ Department of Ophthalmology, University of California, San Francisco, USA ⁴ Department of Ophthalmology and Pacific Vision Foundation, California Pacific Medical Center, San Francisco, USA ⁵ Jules Stein Eye Institute and Department of Ophthalmology, David Geffen School of Medicine at the University of California, Los Angeles, USA

Abstract

Purpose—To characterize the clinical manifestations of cytomegalovirus (CMV) retinitis in northern Thailand.

Design—Prospective, observational cross-sectional study.

Methods—We recorded characteristics of 52 consecutive patients newly diagnosed with CMV retinitis at a tertiary university-based medical center in northern Thailand. Indirect ophthalmoscopy by experienced ophthalmologists was supplemented with fundus photography to determine the proportion of eyes with various clinical features of CMV retinitis.

Results—Of the 52 patients with CMV retinitis, 55.8% were female. All were HIV-positive. The vast majority (90.4%) had started antiretroviral therapy. CMV retinitis was bilateral in 46.2% of patients. Bilateral visual acuity worse than 20/60 was observed in 23.1% of patients. Of 76 eyes with CMV retinitis, 61.8% had zone I disease and 21.6% had lesions involving the fovea. Lesions larger than 25% of the retinal area were observed in 57.5% of affected eyes. CMV retinitis lesions commonly had marked or severe border opacity (47.4% of eyes). Vitreous haze was often present (46.1% of eyes). Visual impairment was more common in eyes with larger retinitis lesions. Retinitis lesion size, used as a proxy for duration of disease, was associated with fulminant appearance (OR 1.24 [1.01 – 1.51]), and marked or severe border opacity (OR 1.36 [1.11 – 1.67]). Based on lesion size, retinitis preceded antiretroviral treatment in each patient.

Conclusions—Patients presenting to a tertiary medical center in northern Thailand have advanced CMV retinitis, possibly due to delayed diagnosis. Earlier screening and treatment of CMV retinitis may limit progression of disease and prevent visual impairment in this population.

© 2011 Elsevier Inc. All rights reserved.

Corresponding Author: Jeremy D Keenan 95 Kirkham Street, Box 0944 F.I. Proctor Foundation University of California, San Francisco San Francisco, CA 94143-0944 Tel: (415) 476-6323 Fax: (415) 476-0527 jeremy.keenan@ucsf.edu.

*These authors contributed equally to this work

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

characteristics; HIV; AIDS; opportunistic infection; Asia

Introduction

Cytomegalovirus (CMV) retinitis is an opportunistic infection affecting severely immunocompromised persons, most commonly those with HIV infection or iatrogenic immunosuppression. The incidence of CMV retinitis has decreased dramatically in industrialized countries due to widespread use of highly active antiretroviral therapy (HAART).¹ However, CMV retinitis is still prevalent in some parts of the world. In particular, CMV retinitis has been observed in as many as one-third of patients with AIDS in areas of Southeast Asia.^{2, 3}

The clinical characteristics of CMV retinitis have been well described in industrialized countries, both before and after the introduction of widespread HAART.⁴⁻⁷ Retinal infection with CMV usually becomes clinically evident at CD4 counts of less than 50 cells/ μ L.⁸ CMV retinitis at higher CD4 counts is uncommon, although active disease can be seen in early immune reconstitution.^{4, 8} Active retinal infection is characterized by progressive white areas of retinal necrosis and edema, with small white satellite lesions at the leading edge of the active retinitis.³ Lesions have often been classified into an indolent/granular form or a fulminant/edematous form, although the severity of opacity may be a more useful clinical description of disease.^{7, 9} Numerous studies have reported the clinical features of CMV retinitis, though these have usually described populations of predominantly white and Latino men from industrialized countries.⁴⁻⁷ The clinical appearance of CMV retinitis has not been well characterized in geographic regions where the HIV epidemic is now most prevalent, including Southeast Asia. Clinical characteristics may be different in Southeast Asia due to differences in health care access and antiretroviral use, as well as cultural norms which may cause patients to delay seeking medical attention unless they have severe illness. In addition, there is emerging evidence that host genetic factors may contribute to expression of CMV disease in patients with AIDS; these genetic factors might differ in Asian patients.¹⁰ In this report, we describe the clinical characteristics of patients and eyes with newly diagnosed, untreated CMV retinitis at an ocular infectious disease clinic in northern Thailand.

Methods

Study Design

We conducted a prospective study at the Ocular Infectious Diseases Clinic at the Maharaj Nakorn Chiang Mai Hospital, a university-based tertiary medical center. From August 7, 2008 until April 9, 2009, all patients presenting for their initial visit at the clinic and not previously treated for CMV retinitis were interviewed and examined according to a pre-specified protocol, with a standardized data form. We documented the characteristics of all patients at presentation, whether or not they were being treated with antiretrovirals. Patients provided demographic and clinical information, including HIV status and date of diagnosis, antiretroviral use and duration of treatment, and most recent and nadir CD4 count. No attempt was made to confirm these self-reported answers. Visual symptoms and visual acuity were assessed by ophthalmic technicians and ophthalmology residents. An ophthalmologist with at least 4 years of experience examining patients with CMV retinitis (SA, SA, or CJ) performed indirect ophthalmoscopy to determine the presence of CMV retinitis, vitreous haze, and retinal detachment. If CMV retinitis was present, the examiner also documented the size of the lesion to the nearest 5% (using indentational indirect ophthalmoscopy if necessary), the zones affected, and whether the lesion appeared to be

active. A detailed retinal drawing was performed for each examined eye. All patients subsequently received fundus photography with a TOPCON TRC-NW 6S camera (TOPCON, Tokyo, Japan), resulting in 9 individual 45° photographs to cover all quadrants of the retina, and 1 composite photograph with an 85° angle of coverage. Photographs were retrospectively examined by one author (JDK) for several features that were not recorded by the examining ophthalmologist, including: retinitis appearance (fulminant/edematous versus indolent/granular), intralesional hemorrhages, frosted branch angiitis, and retinitis involving the optic nerve, vascular arcades, or fovea. Photographs were also reviewed by one author (GNH) for retinitis border opacity.

Definitions

Low vision was defined as best corrected visual acuity worse than 6/18 (20/60), but better than or equal to 3/60 (20/400).¹¹ Blindness was defined as best corrected visual acuity worse than 3/60 (20/400). Unilateral low vision was defined as low vision in one eye, and visual acuity equal to or better than 20/60 in the other. Unilateral blindness was defined as blindness in one eye, and visual acuity equal to or better than 20/400 in the other. CMV retinitis zones were defined according to accepted criteria.¹² Zone 1 included the area within 3000µm of the anatomic macula or within 1500µm of the margin of the optic disc; zone 2 as the area that extends anterior from zone 1 to the clinical equator of the eye; and zone 3 as the remaining retina that extends to the ora serrata. CMV retinitis lesion size was defined as the percentage of retinal area affected by disease, and categorized as <10%, 11-25%, 26-50%, and >50%. CMV retinitis was classified as active or inactive based on the impression of the examining ophthalmologist. Vitreous haze was graded during the clinical examination according to the SUN criteria (4+ if the optic nerve head was obscured, 3+ if the optic nerve head was present but with blurry borders, 2+ if the retinal vessels could be better visualized, and 1+ if the optic nerve head and retinal vessels were even better defined).^{13, 14} Retinal detachment was defined as the presence of any type of retinal detachment detected by indirect ophthalmoscopy. Multifocal disease was defined as the presence of more than one focus of retinitis, as judged from the ophthalmologist's detailed retinal drawing.

The appearance of retinitis was classified according to prior studies.⁷ Briefly, indolent/granular lesions consisted of granular opacification with visible choroidal detail, or opacification only at the border of the lesion, with trace or no hemorrhage, and no vascular sheathing. Fulminant/edematous lesions consisted of dense confluent areas of retinal opacification and the absence of a clear central atrophic area. Border opacity was graded based on standard photographs as mild (1+) if the border was exclusively faint and did not obscure the underlying choroid, or was composed of satellites only; as moderate (2+) in the presence of isolated segments of more dense retinal whitening that partially obscured the underlying choroid; as marked (3+) in the presence of confluent whitening of most of the border that partially obscured the underlying choroid; and as severe (4+) if the opacity was so dense that no choroidal details could be observed.⁷ Intralesional hemorrhages were based on criteria used in prior studies, with the term "minimum" denoting a few scattered punctate spots of blood, "moderate" denoting many spots of blood or occasional blotchy areas of blood not obscuring the underlying structures, and "marked" denoting dense, confluent solid red blood that obscured the view of underlying structures.⁷ Frosted branch angiitis was defined as present if multiple retinal vessels displayed characteristic vascular sheathing in an area remote from a focus of retinitis.¹⁵ Retinitis location was categorized as involving the optic nerve, arcades, or fovea if retinitis affected any part of these structures.

Statistical analysis

Descriptive statistics were performed for demographic and clinical characteristics of patients with CMV retinitis. We calculated proportions for categorical variables, and medians with

interquartile ranges for continuous variables. The Wilcoxon rank sum test was used to test differences in CD4 counts in different populations of patients. We also calculated the proportion of eyes with the clinical signs described above. Results are displayed for the subgroup with visual acuity worse than 20/60 (low vision or worse), and for the subgroup with visual acuity of 20/60 or better (normal vision), as well as for the total population. Fisher's exact test was used to assess for associations between low vision and each of the clinical findings, using a level of significance of $\alpha=0.05$. Backwards stepwise logistic regression was performed using the presence of low vision or worse as the outcome variable, and all clinical signs as explanatory variables, accounting for non-independence of fellow eyes. We performed univariate logistic regression analyses using various signs of clinical severity (categorized as present or absent) as the outcome variable, and lesion size (used as a proxy for duration of retinitis) as a continuous explanatory variable.

We estimated the date of onset of CMV retinitis infection for each patient, based on the lesion size in percentage of retina affected. For these calculations, we estimated the total retinal surface area was 1128mm², assuming a spherical eyeball with an inner scleral radius of 11mm, and an ora serrata 29° anterior to the equator.¹⁶ We assumed a single circular lesion, with a central focus of CMV retinitis, and a rate of progression of 61 μ m per day.⁹ We acknowledge that this technique of determining the date of retinitis onset is imprecise. Therefore, in a sensitivity analysis, we repeated the analysis assuming a faster rate of progression (120 μ m per day), multifocal disease (2 completely separate circular lesions with central foci of CMV retinitis) and a smaller eye (inner scleral radius of 10mm, resulting in a total retinal surface area of 933mm²).⁹ Note that these are conservative assumptions for progression rate, which could underestimate the duration of CMV retinitis infection. The Wilcoxon sign rank test was used to assess whether the estimated duration of disease was different from the duration of antiretroviral therapy. All statistical analyses were performed with Stata 10 (Statacorp, College Station, TX).

Results

Patient characteristics

During the 8 months of the study, 123 patients were examined for the first time at the Ocular Infectious Diseases Clinic, all of whom were infected with HIV. Of the 123 patients, 52 patients with newly diagnosed CMV retinitis and 37 patients without CMV retinitis were prospectively examined. Due to logistical constraints, 34 patients without CMV retinitis were not examined using the prospective data form, and are not discussed in this report.

The median age of the 52 patients with CMV retinitis was 37.5 years (range 14-57 years); about half were female (Table 1). HIV was diagnosed a median of 1.8 years prior to examination. CMV retinitis was a relatively infrequent initial presentation for HIV; only 5 (10%) patients were diagnosed with CMV retinitis within 3 months of being diagnosed with HIV. The vast majority (47/52, 90.4%) of patients diagnosed with CMV retinitis were on antiretroviral therapy at the time of diagnosis. Of patients on antiretrovirals with available data, 41/45 (91%) had been started on antiretrovirals between 1 and 2 months prior, and the remaining 4 (9%) had started treatment less than 1 month prior. Of the 5 patients not on antiretrovirals, 2 had been recently diagnosed, 2 had been lost to follow-up by their internist, and 1 had developed antiretroviral resistance. Of 38 patients who remembered their most recent CD4 count, 24 (63.2%) reported a CD4 count of less than 50 cells/ μ L (range 1-434). Of note, 9 patients (23.7%) reported a recent CD4 count of 100 cells/ μ L or greater. Only 20 patients recalled a CD4 nadir; of those, 17 (85.0%) reported their lowest CD4 count to be less than 50 cells/ μ L. Almost half (24/52, 46.2%) of patients had bilateral CMV retinitis on their initial presentation. There was a high prevalence of visual impairment in this population; visual acuity of worse than 20/60 was observed in both eyes of 12 patients

(23.1%), and one eye of 29 patients (55.8%). Blindness, defined as visual acuity worse than 20/400, was not uncommon. Four patients were bilaterally blind, and 19 patients were unilaterally blind.

Ocular findings on examination

Of 76 eyes diagnosed with CMV retinitis, the median visual acuity was 20/80 (IQR 20/30 to 20/1200), with 43 eyes (56.6%) classified as low vision or worse, and 23 (30.3%) as blind (Table 2). Visual symptoms were present in the vast majority of patients, and usually consisted of blurriness, floaters, or a scotoma. CMV retinitis was commonly located in multiple zones of the retina, though 12 of 76 eyes (15.8%) had retinitis localized solely to zone 3. A wide distribution of CMV retinitis lesion size was observed; the median percentage of the retina affected was 30% (IQR 5 to 90%), and 42 of 74 (56.8%) eyes with available data had lesions affecting more than 25% of the retina. Active inflammatory retinitis was seen in 62 of 71 (87.3%) eyes with available data. The 6 patients with quiescent disease were all taking antiretrovirals, and had a higher recent CD4 count (median 155 [IQR 125-401] in 5 patients with data) compared to patients with active lesions (median CD4 count 26 [IQR 7-50] in 33 patients with data; $p=0.004$, Wilcoxon rank sum test). Multifocal retinitis was noted in 18/76 (23.7%) eyes, and retinal detachment in 5/76 (6.6%) eyes.

Vitreous haze was common, observed in 35 eyes (46.1%). When present, vitreous haze was usually mild, though 13/35 eyes (37.1%) had a grade of 2+ or greater. Of the 13 eyes with at least 2+ vitreous haze, 11 had active CMV retinitis. Vitreous haze was usually observed in the setting of antiretroviral therapy; 11/12 patients with at least 2+ vitreous haze were taking antiretrovirals. Among patients with CMV retinitis, those with 2+ or greater vitreous haze had a higher recent CD4 count (median 38 [IQR 15.5-74] in 8 patients with data) compared with patients without this degree of vitreous haze (median CD4 count 28.5 [IQR 7-125] in 30 patients with data), though this did not constitute a significant difference ($p=0.97$, Wilcoxon rank sum test). The duration of antiretroviral therapy was similar in patients with 2+ vitreous haze or greater (median 38 days [IQR 35-41]) and in those without (median 38 [IQR 32-44], $p=0.99$, Wilcoxon rank sum test).

Ocular findings on photographic review

Retinitis was most often classified as the edematous/fulminant subtype, with 46 of 76 (60.5%) eyes displaying this phenotype. Marked or severe border opacity was present in 36 of 76 (47.4%) eyes. Of the 74 eyes with interpretable photographs, retinitis involved the major vascular arcades in 42 (56.8%), optic disc in 17 (23.0%), and fovea in 16 (21.6%); intralésional hemorrhages were observed in 47 (63.5%) eyes and frosted branch angiitis in 10 (13.5%).

Risk factors for low vision and severe presentation of CMV retinitis

Eye findings were tabulated stratified by vision status (Table 2). Those eyes classified as low vision or worse were more likely to have the following findings: more posterior zone of involvement, larger retinitis lesion size, retinitis affecting the vascular arcades or fovea, and vitreous haze (Table 2). In a backwards stepwise logistic regression, lesion size was the only significant predictor of low vision or worse (OR 3.84 [95% CI 0.81 – 18.18] for lesions 11-25% of retinal area, OR 5.60 [95% CI 1.48 – 21.13] for lesions 26-50%, and OR 12.80 [95% CI 2.90 – 56.58] for lesions >50%, compared to lesions ≤10% retinal area; $p=0.007$). Analyses restricted to the 62 eyes with active retinitis did not change these conclusions (data not shown).

Using lesion size as a proxy for duration of retinitis, we created logistic regression models to determine whether the duration of retinitis was a significant predictor of several markers of

severe disease. In these analyses, larger lesion size was significantly associated with foveal involvement (OR 1.26 [95% CI 1.02 – 1.56] per 10% increase in lesion size), optic disc involvement (OR 1.27 [1.04 – 1.55]), fulminant appearance (OR 1.24 [1.01 – 1.51]), and marked (3+) or severe (4+) border opacity (OR 1.36 [1.11 – 1.67]). There was also a greater odds of retinal detachment with increasing lesion size, though this relationship did not achieve statistical significance (OR 1.36 [95% CI 0.98 – 1.90] per 10% increase in lesion size).

Estimated date of retinitis onset

We estimated the date of onset of cytomegalovirus retinitis, using lesion size as a guide. The median date of onset was 24.7 weeks prior, assuming a single retinal lesion with a rate of progression of 61 μ m per day. Of the 61 eyes with complete data, the median estimated date of CMV retinitis onset preceded the date of starting antiretroviral therapy (24.7 weeks prior versus 5.4 weeks prior, $p < 0.0001$, Wilcoxon sign rank test). In a sensitivity analysis with even more conservative assumptions (faster progression rate of 120 μ m per day, multifocal disease with 2 lesions, and a smaller eye with an inner scleral radius of 10mm), the estimated median date of onset was 7.9 weeks prior—still earlier than the initiation of antiretrovirals ($p < 0.0001$, Wilcoxon sign rank test).

Other ocular disease

Although not the focus of the study, clinicians noted when ocular disease other than CMV retinitis were present. Of the 102 eyes without CMV retinitis that were prospectively examined, HIV retinopathy was observed in 10 (9.8%), cataract in 5 (4.9%), and optic neuropathy in 3 (2.9%).

Discussion

In patients with HIV seen for the first time at a referral ophthalmology clinic in northern Thailand, CMV retinitis was severe at presentation. Roughly half of referred patients had bilateral CMV retinitis, and almost half were blind in at least one eye. CMV retinitis often appeared as a fulminant retinitis with marked or severe border opacity, often involving a large percentage of the retina, with frequent involvement of zone 1, and not uncommonly, involvement of the fovea and optic disc. Vitreous haze was commonly observed.

The CMV retinitis observed in this Thai population differed in several ways from that reported in western populations. First, the sociodemographics of disease were different, with more women affected in this study (56%) compared to previous studies in the United States (5-36% female). Although this likely reflects the underlying HIV epidemic in each setting, we still observed more females than expected, since roughly 40% of HIV-infected persons in Thailand are thought to be female.¹⁷ There is evidence that females may have relatively better access to HIV care than males in northern Thailand, which may explain the higher numbers of females seen.¹⁸ In addition, a higher proportion of patients were on antiretroviral therapy in this study (90%) compared with previous studies in the United States (51-63%). Patients had a delay of roughly 1.5 years from HIV diagnosis to initiation of antiretroviral therapy, suggesting that they did not meet criteria for treatment at their initial presentation. (The World Health Organization [WHO] recommends starting treatment at a CD4 count below 350 cells/ μ L or in WHO clinical stage 3 or 4.¹⁹) A delay of this magnitude is consistent with the experience of others in northern Thailand.¹⁸

The severity of CMV retinitis at initial presentation in this Thai population was arguably worse than that observed in western populations. In comparison, studies of incident CMV retinitis conducted in the United States both before⁵⁻⁷ and after^{4, 6} the introduction of

widespread antiretroviral therapy found less bilaterality of retinitis (26-39%, compared to 46% in this study), smaller retinitis lesions (median, 17-23% of retina, compared to 30% in this study), less frequent zone I involvement (41-53%, compared to 62% in this study), less foveal involvement (12-13%, compared to 22% in this study), a better median visual acuity (20/20 to 20/30, compared to 20/80 in this study), and a smaller proportion of fulminant retinitis lesions (23-46%, compared to 61% in this study). It is unclear whether this degree of advanced disease is typical in other Asian countries, though other reports from Asia have noted a similar amount of bilateral disease, posterior involvement, retinal detachment, and blindness.²⁰⁻²⁵

We hypothesized that the more severe presentation of this Thai population may have been due to a delay in diagnosis. In support of this hypothesis, we found that larger lesion size, which is thought to be a proxy for duration of retinitis,⁵ was associated with several measures of advanced or severe disease, such as foveal involvement, optic disc involvement, and $\geq 3+$ border opacity. Retinal detachment was also more common as lesion size increased, though this relationship was not statistically significant. This suggests that more severe disease occurred in patients with a longer duration of CMV retinitis, consistent with a delay in diagnosis. We can only speculate on other factors that could explain the severe presentation found in this population, though viral and host factors could potentially play a role. For example, there have been reports of an association between CMV strain and CMV retinitis, and also between host genetic factors and CMV retinitis.^{10, 26} In addition, HIV infects retinal cells and enhances CMV infection in vitro, raising the possibility that HIV subtype could play a role in retinitis phenotype.^{27, 28}

We observed substantial vitreous inflammation in many patients in our study. Although anterior vitreous cells were not uncommonly observed in eyes with active CMV retinitis in western countries in the pre-HAART era,^{5, 29, 30} vitreous haze sufficient to reduce vision was not frequently reported. In contrast, almost half of eyes with CMV retinitis in the current study had vitreous haze, and 17% had 2+ or greater vitreous haze. We assume that the more prominent vitreous haze observed in this study reflects immune recovery uveitis following the institution of antiretroviral therapy, a phenomenon that has been reported in patients recently started on antiretroviral therapy.^{31, 32} Although immune recovery uveitis usually occurs at CD4 counts higher than those observed in this study, there have been case reports from Asia describing vigorous inflammatory reactions at low CD4 counts.³³⁻³⁵ In addition, the CD4 counts reported in this study were self-reported, and therefore subject to recall bias; it is possible that the actual CD4 counts were higher than reported. Furthermore, compared with earlier studies in industrialized countries, we observed a higher proportion of patients on antiretroviral therapy and a lower proportion of patients experiencing antiretroviral failure.^{4, 6} This means that a higher proportion of patients in our study were at risk for developing immune recovery uveitis, which may explain why we observed more vitreous haze relative to these previous studies.

The vitreous inflammation observed in this study may have resulted from initiation of antiretroviral therapy in patients with pre-existing CMV retinitis. In our study population, over 90% of patients had been started on antiretroviral therapy, and the vast majority had been on antiretroviral medications for 1-2 months. In fact, it was unusual for patients on antiretroviral therapy for less than 1 month to present for examination. Furthermore, almost one-quarter of the patients in our study reported a CD4 count of ≥ 100 cells/ μ L. The occurrence of CMV retinitis within 2 months of starting antiretroviral therapy has been observed by others, often in patients with CD4 counts greater than 100 cells/ μ L.^{8, 31} Others have noted a vitritis in some cases of CMV retinitis diagnosed in the months following the initiation of antiretroviral therapy.³¹ We suspect that most of the patients in our study population had undiagnosed CMV retinitis prior to initiation of antiretroviral therapy.³¹ In

support of this hypothesis, calculations based on the size of CMV retinitis lesions suggested that all patients had an onset of CMV retinitis which preceded initiation of antiretroviral therapy. Although these calculations are imprecise, we came to the same conclusion even if very conservative assumptions were made. Partial immune reconstitution may have occurred during the first 2 months of therapy, allowing a vigorous inflammatory response in the vitreous and retina.³⁶ Conceivably, patients became symptomatic and sought ophthalmologic care only after the vitreo-retinal inflammation became severe, presumably after 1-2 months of antiretroviral therapy.

A delay in diagnosis of CMV retinitis could have a negative impact in at least two ways. First, advanced retinal infection can directly cause vision loss. We found that larger lesions and lesions involving the fovea and vascular arcades were associated with low vision. Second, more severe CMV retinitis is thought to increase the risk of immune recovery uveitis.³⁷ Thus, diagnosis of CMV retinitis at an earlier stage should be a priority. Earlier screening is difficult in Thailand, due to a shortage of ophthalmologists outside of highly populated areas. Challenges surrounding early CMV retinitis screening likely extend to other emerging and developing countries in Asia and Africa, which together account for the greatest burden of HIV worldwide.⁴⁰ New strategies for earlier CMV retinitis screening should be explored in these settings, including training HIV clinicians in indirect ophthalmoscopy, and remote diagnosis by telemedicine.^{3, 41}

We acknowledge several limitations to this study. First, we used self-report for CD4 counts, HIV history, and antiretroviral history, resulting in incomplete data that is subject to recall bias. Second, the calculations used to determine date of CMV retinitis onset are imprecise, and should be interpreted with caution. However, even conservative assumptions did not change the conclusions of these calculations. Finally, this study was conducted at a tertiary medical center in Thailand, which could have resulted in referral bias. However, very few if any other clinics in northern Thailand diagnose and treat CMV retinitis. While it is possible that patients with less advanced disease do not seek ophthalmologic care altogether, it is probable that those patients living in Northern Thailand who seek care are seen at our study site. Further study outside of a tertiary medical center is warranted to determine the burden and clinical features of CMV retinitis in the Thai HIV population at-large.

In conclusion, we report the clinical characteristics of patients and eyes with CMV retinitis seen in a referral clinic in northern Thailand. CMV retinitis was usually seen between 1 and 2 months after starting antiretroviral therapy, perhaps indicating the time for symptoms to develop and a referral to be made. Retinitis was often bilateral and of fulminant appearance, with marked border opacity. Large areas of the retina were often affected, frequently with optic nerve, macula, and fovea involvement. Vitreous haze was frequently present. Blindness was common. Early screening for CMV retinitis should be an important component of HIV care for at-risk populations in Thailand and other developing countries, since anti-CMV treatment started before or concurrently with initiation of antiretroviral therapy may limit vision loss.

Acknowledgments

A) Funding/support: Funding for this project was provided by the University of California, San Francisco-Gladstone Institute of Virology and Immunology Center for AIDS Research, the University of California at San Francisco Research Evaluation and Allocation Committee, That Man May See, the Littlefield Trust, the Peierls Foundation, and a number of grateful patients. This project was also supported by NIH/NCRR/OD UCSF-CTSI KL2 RR024130, and NIH/NEI K23EY019071.

B) Financial Disclosures: None of the authors report financial disclosures.

C) Contributions to authors: Study design (SA, JDK, SA, CK, AHS, DH, GNH, TPM); conduct of study (SA, JDK, SA, CJ, CK, TPM); collection of data (SA, JDK, SA, CJ, CK, TPM); management of data (SA, JDK, SA, CK); analysis of data (JDK); interpretation of data (SA, JDK, DH, GNH, TPM); preparation of manuscript (SA, JDK), review of manuscript (SA, JDK, SA, CJ, CK, AHS, DH, GNH, TPM), and approval of manuscript (SA, JDK, SA, CJ, CK, AHS, DH, GNH, TPM).

D) Statement about conformity with author information: Institutional review board approval was obtained at the University of California, San Francisco, and Chiang Mai University, Chiang Mai, Thailand. The study adhered to the tenets of the Declaration of Helsinki. All study participants gave written informed consent.

E) Other acknowledgements: None.

Biography

Biosketch: Dr. Somsanguan Ausayakhun, MD, is Professor of Ophthalmology and Head of the Division of Cytomegalovirus Retinitis and the Division of Dry Eye and Allergy, Department of Ophthalmology, Faculty of Medicine, Chiang Mai University. Her primary research interests include cornea and uveitis; she runs a busy ocular infectious diseases clinic in Chiang Mai.

References

1. Jacobson MA, Stanley H, Holtzer C, Margolis TP, Cunningham ET. Natural history and outcome of new AIDS-related cytomegalovirus retinitis diagnosed in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2000; 30(1):231–3. [PubMed: 10619774]
2. Ausayakhun S, Watananikorn S, Ittipunkul N, Chaidaroon W, Patikulsila P, Patikulsila D. Epidemiology of the ocular complications of HIV infection in Chiang Mai. *J Med Assoc Thai*. 2003; 86(5):399–406. [PubMed: 12859094]
3. Heiden D, Ford N, Wilson D, et al. Cytomegalovirus retinitis: the neglected disease of the AIDS pandemic. *PLoS Med*. 2007; 4(12):e334. [PubMed: 18052600]
4. Holland GN, Vaudaux JD, Shiramizu KM, et al. Characteristics of untreated AIDS-related cytomegalovirus retinitis. II. Findings in the era of highly active antiretroviral therapy (1997 to 2000). *Am J Ophthalmol*. 2008; 145(1):12–22. [PubMed: 18154751]
5. Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial: 5. Clinical features of cytomegalovirus retinitis at diagnosis. Studies of ocular complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. *Am J Ophthalmol*. 1997; 124(2):141–57. [PubMed: 9262538]
6. Jabs DA, Van Natta ML, Kempen JH, et al. Characteristics of patients with cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Am J Ophthalmol*. 2002; 133(1):48–61. [PubMed: 11755839]
7. Holland GN, Vaudaux JD, Jeng SM, et al. Characteristics of untreated AIDS-related cytomegalovirus retinitis. I. Findings before the era of highly active antiretroviral therapy (1988 to 1994). *Am J Ophthalmol*. 2008; 145(1):5–11. [PubMed: 18154750]
8. Michelet C, Arvieux C, Francois C, et al. Opportunistic infections occurring during highly active antiretroviral treatment. *AIDS*. 1998; 12(14):1815–22. [PubMed: 9792382]

9. Holland GN, Shuler JD. Progression rates of cytomegalovirus retinopathy in ganciclovir-treated and untreated patients. *Arch Ophthalmol*. 1992; 110(10):1435–42. [PubMed: 1329703]
10. Deghaide NH, deRodrigues ML, Castelli EC, Mendes-Junior CT, Figueiredo JF, Donadi EA. Tumor necrosis factor region polymorphisms are associated with AIDS and with cytomegalovirus retinitis. *AIDS*. 2009; 23(13):1641–7. [PubMed: 19542865]
11. World Health Organization. International statistical classification of diseases, injuries and causes of death. tenth revision. World Health Organization; Geneva: 1993.
12. Holland GN, Buhles WC Jr, Mastre B, Kaplan HJ. A controlled retrospective study of ganciclovir treatment for cytomegalovirus retinopathy. Use of a standardized system for the assessment of disease outcome. UCLA CMV Retinopathy. Study Group. *Arch Ophthalmol*. 1989; 107(12):1759–66. [PubMed: 2556989]
13. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol*. 2005; 140(3):509–16. [PubMed: 16196117]
14. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology*. 1985; 92(4):467–71. [PubMed: 4000641]
15. Spaide RF, Vitale AT, Toth IR, Oliver JM. Frosted branch angiitis associated with cytomegalovirus retinitis. *Am J Ophthalmol*. 1992; 113(5):522–8. [PubMed: 1349456]
16. Weinberg DV, Holbrook JT, Hubbard LD, Davis MD, Jabs DA, Holland GN. Clinician versus reading center assessment of cytomegalovirus retinitis lesion size. *Ophthalmology*. 2005; 112(4):559–66. [PubMed: 15808244]
17. UNAIDS. [accessed October 6, 2011] HIV and AIDS estimates. 2009. <http://www.unaids.org/en/regionscountries/countries/thailand/>
18. Le Coeur S, Collins IJ, Pannetier J, Lelievre E. Gender and access to HIV testing and antiretroviral treatments in Thailand: why do women have more and earlier access? *Soc Sci Med*. 2009; 69(6):846–53. [PubMed: 19573965]
19. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision. World Health Organization; Geneva, Switzerland: 2010.
20. Ho PC, Farzavandi SK, Kwok SK, Lam DS, Lee SS, Li PC. Ophthalmic complications in AIDS in Hong Kong. *J Hong Kong Med Assoc*. 1994; 46(2):117–20.
21. Sahu DK, Namperumalsamy P, Walimbe P, Rajalakshmi C. Ocular manifestations of HIV infection/AIDS in south Indian patients. *Indian J Ophthalmol*. 1999; 47(2):79–85.
22. Biswas J, Joseph A, Raizada S, Kumamsamy N, Solomon S. Ophthalmic manifestations of human immunodeficiency virus (HIV) infection in India. *Indian J Ophthalmol*. 1999; 47(2):87–93.
23. Biswas J, Madhavan HN, George AE, Kumarasamy N, Solomon S. Ocular lesions associated with HIV infection in India: a series of 100 consecutive patients evaluated at a referral center. *Am J Ophthalmol*. 2000; 129(1):9–15. [PubMed: 10653406]
24. Pathai S, Deshpande A, Gilbert C, Lawn SD. Prevalence of HIV-associated ophthalmic disease among patients enrolling for antiretroviral treatment in India: a cross-sectional study. *BMC Infect Dis*. 2009; 9:158. [PubMed: 19775470]
25. Lai TY, Wong RL, Luk FO, Chow VW, Chan CK, Lam DS. Ophthalmic manifestations and risk factors for mortality of HIV patients in the post-highly active antiretroviral therapy era. *Clin Experiment Ophthalmol*. 2011; 39(2):99–104. [PubMed: 20796263]
26. Shepp DH, Match ME, Ashraf AB, Lipson SM, Millan C, Pergolizzi R. Cytomegalovirus glycoprotein B groups associated with retinitis in AIDS. *J Infect Dis*. 1996; 174(1):184–7. [PubMed: 8655991]
27. Skolnik PR, Kosloff BR, Hirsch MS. Bidirectional interactions between human immunodeficiency virus type 1 and cytomegalovirus. *J Infect Dis*. 1988; 157(3):508–14. [PubMed: 2830343]
28. Skolnik PR, Pomerantz RJ, de la Monte SM, et al. Dual infection of retina with human immunodeficiency virus type 1 and cytomegalovirus. *Am J Ophthalmol*. 1989; 107(4):361–72. [PubMed: 2539019]

29. Rosberger DF, Heinemann MH, Friedberg DN, Holland GN. Uveitis associated with human immunodeficiency virus infection. *Am J Ophthalmol.* 1998; 125(3):301–5. [PubMed: 9512146]
30. Palestine AG, Rodrigues MM, Macher AM, et al. Ophthalmic involvement in acquired immunodeficiency syndrome. *Ophthalmology.* 1984; 91(9):1092–9. [PubMed: 6093020]
31. Jacobson MA, Zegans M, Pavan PR, et al. Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy. *Lancet.* 1997; 349(9063):1443–5. [PubMed: 9164318]
32. Zegans ME, Walton RC, Holland GN, O'Donnell JJ, Jacobson MA, Margolis TP. Transient vitreous inflammatory reactions associated with combination antiretroviral therapy in patients with AIDS and cytomegalovirus retinitis. *Am J Ophthalmol.* 1998; 125(3):292–300. [PubMed: 9512145]
33. Kuppermann BD, Holland GN. Immune recovery uveitis. *Am J Ophthalmol.* 2000; 130(1):103–6. [PubMed: 11004267]
34. Alp MN, Baykam N, Kural G. Immune recovery uveitis associated with highly active antiretroviral therapy in a patient with CMV retinitis and AIDS despite a low CD4+ T cell count: case report and a review of the literature. *Int Ophthalmol.* 2010; 30(2):183–9. [PubMed: 19198761]
35. Gan NY, Teoh SC. Haemorrhagic hypertensive hypopyon uveitis in early immune reactivation uveitis. *Eye (Lond).* 2010; 24(2):383. [PubMed: 19407838]
36. Nussenblatt RB, Lane HC. Human immunodeficiency virus disease: changing patterns of intraocular inflammation. *Am J Ophthalmol.* 1998; 125(3):374–82. [PubMed: 9512156]
37. Kempen JH, Min YI, Freeman WR, et al. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. *Ophthalmology.* 2006; 113(4):684–94. [PubMed: 16581429]
38. Holland GN. AIDS and ophthalmology: the first quarter century. *Am J Ophthalmol.* 2008; 145(3):397–408. [PubMed: 18282490]
39. Ortega-Larrocea G, Espinosa E, Reyes-Teran G. Lower incidence and severity of cytomegalovirus-associated immune recovery uveitis in HIV-infected patients with delayed highly active antiretroviral therapy. *AIDS.* 2005; 19(7):735–8. [PubMed: 15821403]
40. The United Nations Joint Programme of HIV (UNAIDS). UNAIDS report on the global AIDS epidemic, 2010. UNAIDS; Geneva: 2010.
41. Ausayakhun S, Skalet AH, Jirawison C, et al. Accuracy and reliability of telemedicine for diagnosis of cytomegalovirus retinitis. *Am J Ophthalmol.* Forthcoming.

Table 1

Clinical and demographic characteristics of 52 patients presenting with untreated CMV retinitis to an ophthalmology clinic in Chiang Mai, Thailand

Characteristic	N ^a	Proportion, %, or Median (IQR)
Age, years; median (IQR)	52	37.5 (32.5-44)
Female	52	55.8%
HIV +	52	100%
Diagnosed ≤ 3 months ago	52	9.6%
Diagnosed ≤ 6 months ago	52	38.5%
Years since HIV diagnosis; median (IQR)	52	1.8 (0.3-7.4)
Currently on antiretroviral	52	90.4%
Started antiretroviral < 1 month ago	45	8.9%
Started antiretroviral < 2 months ago	45	100%
Duration of therapy, weeks; median (IQR)	45	5.4 (4.7-6.3)
Most recent CD4 count ^b		
Median (IQR), per μ L	38	32.5 (7-98)
<50 cells/ μ L	38	63.2%
Nadir CD4 count ^b		
Median (IQR), per μ L	20	25 (6-37.5)
<50 cells/ μ L	20	85.0%
CMV retinitis		
Bilateral	52	46.2%
Unilateral ^c	52	53.8%
Right eye	28	46.4%
Left eye	28	53.6%
Low vision ^d		
Bilateral	52	5.8%
Unilateral	52	28.8%
Blindness ^e		
Bilateral	52	7.7%
Unilateral, with contralateral low vision	52	9.6%
Unilateral	52	26.9%

^aNumber of patients with complete data

^bCD4 count values are by patient report

^cIn four patients classified as unilateral CMV, the presence of CMV retinitis in the contralateral eye could not be determined

^dLow vision is defined as best corrected visual acuity worse than 20/60 but better or equal to 20/400

^eBlindness is defined as best corrected visual acuity worse than 20/400 IQR = interquartile range

Table 2

Clinical characteristics of 76 eyes with untreated CMV retinitis from an ophthalmology clinic in Chiang Mai, Thailand

Characteristic	All eyes		Low vision or worse ^a		Normal vision		P-value ^b
	%	N	%	N	%	N	
Visual acuity							
Low vision	26.3%	20/43	46.5%	0/33	0%		
Blindness	30.3%	23/43	53.5%	0/33	0%		
Visual symptoms							
Any symptoms	90.8%	43/43	100%	26/33	78.8%		0.002
Blurriness	84.2%	42/43	97.7%	22/33	66.7%		0.06
Floaters	17.1%	8/43	18.6%	5/33	15.2%		1.00
Flashes	7.9%	3/43	7.0%	3/33	9.1%		0.67
Scotoma	10.5%	5/43	11.6%	3/33	9.1%		0.65
Retinitis Location							
Involving optic disc	23.0%	13/41	31.7%	4/33	12.1%		0.06
Involving arcades	56.8%	32/41	78.0%	10/33	30.3%		<0.001
Involving fovea	21.6%	16/41	39.0%	0/33	0%		<0.001
Most Posterior Zone							0.04
Zone 1	61.8%	31/43	72.1%	16/33	48.5%		
Zone 2	22.4%	9/43	20.9%	8/33	24.2%		
Zone 3	15.8%	3/43	7.0%	9/33	27.3%		
Lesion size							0.003
≤0%	28.4%	5/41	12.2%	16/33	48.5%		
11-25%	14.9%	6/41	14.6%	5/33	15.2%		
26-50%	29.7%	14/41	34.1%	8/33	24.2%		
>50%	7.0%	16/41	39.0%	4/33	12.1%		
Retinitis Appearance							0.37
Granular	11.8%	7/43	16.3%	2/33	6.1%		
Fulminant	60.5%	26/43	60.5%	20/33	60.6%		
Indeterminant	27.6%	10/43	23.3%	11/33	33.3%		
Border opacity							0.06

Characteristic	All eyes		Low vision or worse ^a				Normal vision		P-value ^b
	%	N	%	N	%	N	%	N	
1+	5.3%	0/43	0%	4/33	0%	4/33	12.1%	12.1%	
2+	9.2%	3/43	7.0%	4/33	7.0%	4/33	12.1%	12.1%	
3+	25.0%	12/43	27.9%	7/33	27.9%	7/33	21.2%	21.2%	
4+	22.4%	13/43	30.2%	4/33	30.2%	4/33	12.1%	12.1%	
Unknown	38.2%	15/43	34.9%	14/33	34.9%	14/33	42.4%	42.4%	
Intralesional hemorrhage									0.10
None	36.5%	10/41	24.4%	17/33	24.4%	17/33	51.5%	51.5%	
Minimum	18.9%	9/41	22.0%	5/33	22.0%	5/33	15.2%	15.2%	
Moderate	20.3%	9/41	22.0%	6/33	22.0%	6/33	18.2%	18.2%	
Marked	24.3%	13/41	31.7%	5/33	31.7%	5/33	15.2%	15.2%	
Vitreous haze									0.04
None	53.9%	18/43	41.9%	23/33	41.9%	23/33	69.7%	69.7%	
Grade 1+	28.9%	14/43	32.6%	8/33	32.6%	8/33	24.2%	24.2%	
Grade 2+	13.2%	9/43	20.9%	1/33	20.9%	1/33	3.0%	3.0%	
Grade 3+	3.9%	2/43	4.7%	1/33	4.7%	1/33	3.0%	3.0%	
Other characteristics									
Active CMVR	87.3%	34/39	87.2%	28/32	87.2%	28/32	87.5%	87.5%	1.00
Frosted branch Angitis	13.5%	6/41	14.6%	4/33	14.6%	4/33	12.1%	12.1%	1.00
Multifocal retinitis	23.7%	9/43	20.9%	9/33	20.9%	9/33	27.3%	27.3%	0.59
Retinal detachment	6.6%	5/43	11.6%	0/33	11.6%	0/33	0%	0%	0.07

^aLow vision defined as visual acuity worse than 20/60; normal vision as 20/60 or better

^bFisher's exact test comparing eyes with normal vision to eyes with low vision or worse.