The Prevalence and Incidence of Epiretinal Membranes in Eyes With Inactive Extramacular CMV Retinitis

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PURPOSE. To determine the prevalence and incidence of epiretinal membranes (ERM) in eyes with inactive extramacular cytomegalovirus (CMV) retinitis in patients with acquired immune deficiency syndrome (AIDS).

METHODS. A case–control report from a longitudinal multicenter observational study by the Studies of the Ocular Complications of AIDS (SOCA) Research Group. A total of 357 eyes of 270 patients with inactive CMV retinitis and 1084 eyes of 552 patients with no ocular opportunistic infection (OOI) were studied. Stereoscopic views of the posterior pole from fundus photographs were assessed at baseline and year 5 visits for the presence of macular ERM. Generalized estimating equations (GEE) logistic regression was used to compare the prevalence and 5-year incidence of ERM in eyes with and without CMV retinitis at enrollment. Crude and adjusted logistic regression was performed adjusting for possible confounders. Main outcome measures included the prevalence, incidence, estimated prevalence, and incidence odds ratios.

RESULTS. The prevalence of ERM at enrollment was 14.8% (53/357) in eyes with CMV retinitis versus 1.8% (19/1084) in eyes with no OOI. The incidence of ERM at 5 years was 18.6% (16/86) in eyes with CMV retinitis versus 2.4% (6/253) in eyes with no OOI. The crude odds ratio (OR) (95% confidence interval, CI) for prevalence was 9.8 (5.5–17.5) (P < 0.01). The crude OR (95% CI) for incidence was 9.4 (3.2–27.9) (P < 0.01).

CONCLUSIONS. A history of extramacular CMV retinitis is associated with increased prevalence and incidence of ERM formation compared to what is seen in eyes without ocular opportunistic infections in AIDS patients.

Keywords: CMV retinitis, epiretinal membrane, prevalence, incidence, AIDS

Cytomegalovirus (CMV) retinitis is a common ocular opportunistic infection (OOI) resulting in visual loss among patients with the acquired immune deficiency syndrome (AIDS).1 Although the use of combination antiretroviral therapy has reduced the incidence of CMV retinitis by approximately 80%,2–4 the risk of vision loss among patients with CMV retinitis, including those with inactive CMV retinitis, remains substantial when compared to patients without CMV retinitis.5,6

Vision loss attributed to CMV retinitis has been well documented and occurs most commonly as a result of direct macular tissue destruction (e.g., full-thickness retinal necrosis) and/or secondarily as part of rhegmatogenous retinal detachment.7–9 A cause of visual impairment observed in patients who have undergone immune recovery and have inactive extramacular CMV retinitis is immune recovery uveitis (IRU), which may cause visual impairment from active intraocular inflammation (i.e., vitritis) or its attendant structural ocular complications such as cataract, macular edema, proliferative retinopathy, and epiretinal membrane (ERM) formation.4,10–17 Retinal imaging studies have demonstrated vitreoretinal abnormalities in inactive CMV retinitis. In a recent pilot study, retina adjacent to inactive CMV retinitis scars appeared to show a higher frequency of vitreoretinal traction and ERM formation.18

The purpose of this study is to report the prevalence and incidence of ERM in eyes with inactive extramacular CMV retinitis in patients with AIDS enrolled in the Longitudinal Studies of Ocular Complications of AIDS (LSOCA). We hypothesized that eyes with a history of CMV retinitis were more likely to develop ERM compared to eyes without OOI and that ERM may be present in the retinal areas free of CMV retinitis scar.

METHODS

Study Subjects

LSOCA is a prospective observational study of patients with AIDS conducted entirely within the era of highly active antiretroviral therapy (HAART). Patients with diagnosis of AIDS aged 13 years or older were enrolled, regardless of immunologic or CMV retinitis status. Acquired immune deficiency...
syndrome diagnosis was according to the 1993 Centers for Disease Control and Prevention Revised Surveillance Case Definition. This study was approved by the Institutional Review Board at each participating center and the three resource centers. The study was conducted in compliance with the Declaration of Helsinki. All patients gave written informed consent prior to participating in the study.

Patients were enrolled with or without CMV retinitis; data were collected on medication use and comorbidities, and detailed ophthalmologic evaluations, including fundus photography, were performed. Film and digital equipment and photographers at the participating clinical centers were certified, based on submission of a set of sample images, by a centralized Fundus Photograph Reading Center (FPRC) at the Department of Ophthalmology and Visual Sciences, University of Wisconsin-Madison. Specific imaging protocol included one central stereoscopic (posterior pole) and eight peripheral monoscopic 50° or 60° views, extending nearly to the equator. These retinal photographs are sent to the reading center for evaluation of ocular complications of AIDS, especially CMV retinitis, by trained and certified graders (Studies of the Ocular Complications of AIDS Research Group, SOCA cytomegalovirus retinitis grading protocol, 1997; available from the National Technical Information Services, US Department of Commerce, 5285 Port Royal Road, Springfield, VA, USA; NTIS Accession no. PB97-192082).

Topography and Definition of Vitreoretinal Abnormalities

The location and extent of CMV retinitis is assessed using standard grid templates. The LSOCA grid demarcates the retinal regions into three contiguous zones. Zone 1 corresponds to an area of 2 disc diameters (DD) (3600 μm) from the center of macula and 1 DD (1800 μm) from the margins of the optic disc. Zone 2 extends from zone 1 to the vortex veins, and zone 3 extends from zone 2 to the ora serrata.19 Zone 2 is further divided into eight peripheral sectors (corresponding to the eight peripheral photographic fields). The proportionate areas represented by zone 1 and zone 2 are 22 disc areas (DA) and 279 DA of the posterior pole, respectively, out of a total 394 DA of a known total human retinal area (Fig. 1).

In this report, we focus on the ERM in zone 1 in eyes with extramacular CMV retinitis using stereoscopic views of the posterior pole (Fig. 2). A total 1441 eyes were assessed at enrollment. Eyes at enrollment with CMV retinitis in zone 1 or diagnosed with herpetic retinitis, toxoplasmic retinitis, or choroiditis were excluded. Due to correlation of eyes in the same patient, generalized estimating equations (GEE) logistic regression was used to compare the prevalence and 5-year incidence of ERM in eyes with and without CMV retinitis at enrollment.

Eyes diagnosed with ERM at enrollment were excluded from the calculation of 5-year incidence. Patients in the No-OOI group who were diagnosed with CMV retinitis within the 5 years of follow-up also were excluded. Crude and adjusted logistic regression was performed adjusting for age. Karnofsky score, HIV viral load, CD4+ T-cell count, and nadir CD4+ T-cell count.

Patient- and eye-specific risk factors for time-to-event analysis of incident ERM were evaluated in the CMV retinitis group. Person-time was calculated from enrollment to the first reported event of ERM during follow-up or last follow-up date for the patients who were not diagnosed with ERM. The following risk factors were evaluated: newly diagnosed CMV retinitis cases (diagnosed within the 45 days of enrollment) versus longstanding cases, eyes affected with one zone (zone 2 or 3) versus both the zones), presence of an active CMV retinitis border, number of lesions in the affected eye, CD4+ T-cell count, HIV viral load, and age. Cox regression with staggered entries20 was used to estimate the hazard ratios and 95% confidence intervals (CIs). SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA) and STATA version 12.1 (STATA Corp., College Station, TX, USA) were used for the analyses.

Results

The comparison of patient characteristics at enrollment between 357 eyes from 270 patients with zone(s) 2/3 CMV retinitis (e.g., extramacular CMV retinitis) versus 1084 eyes from 552 patients with no OOI is shown in Table 1. The overall mean (range) age of the 822 patients was 44 years (38–51), with 80.7% male, 42.7% white, and 60.6% with higher than high school education. As compared to patients with no OOI, patients with CMV retinitis were significantly younger but were similar with respect to sex, race, and education. In addition, patients with CMV retinitis had significantly lower Karnofsky score, CD4+ T-cell count, and nadir CD4+ T-cell count and higher HIV viral load but were similar with respect to employment and prevalence of self-reported tuberculosis, syphilis, and hepatitis as compared to patients with no OOI.

The prevalence of ERM at enrollment was 14.8% (53/357) in eyes with CMV retinitis versus 1.8% (19/1084) in eyes with no OOI. The crude odds ratio (OR) (95% CI) was 9.8 (5.5–17.5) (P < 0.01). The OR (95% CI) adjusting for age, Karnofsky score, HIV viral load, and current and nadir CD4+ T-cell count was 11.1 (5.6–22.3) (P < 0.01) (Table 2).

Among eyes without ERM at enrollment, there were 86 eyes from 80 patients with CMV retinitis and 253 eyes from 131 patients with no OOI graded for ERM at 5 years. The incidence of ERM at years was 18.6% (16/86) in eyes with CMV retinitis versus 2.4% (6/253) in eyes with no OOI. The crude OR (95% CI) was 9.4 (3.2–27.9) (P < 0.01). The OR (95% CI) adjusted for age, Karnofsky score, HIV viral load, and current and nadir CD4+ T-cell count was 9.6 (3.4–27.9) (P < 0.01) (Table 3).

Within the subgroup of eyes with CMV retinitis, the incidence of ERM at 5 years was compared among CMV retinitis-specific risk factors, including time since diagnosis, activity, zone, bilaterality, and number of lesions, as well as patient-specific risk factors including CD4+ T-cell count, HIV viral load, and age (Table 4). The relative rate (95% CI) of incidence of ERM at 5 years comparing eyes with newly diagnosed versus longstanding CMV retinitis was 2.6 (1.2–5.5).
There were no other significant risk factors among eyes with CMV retinitis for incidence of ERM.

Four LSOCA participants were eligible for cataract surgery out of the 201 participants who were at risk for ERM at 5 years (3/131 patients [253 eyes] in the No-OOI group and 1/70 participants [86 eyes] in the OOI group) \((P = 0.39)\). Retinal detachment (RD) surgery was necessary in 9 eyes in the No-OOI group and in 27 eyes in the OOI group \((P < 0.001)\). Laser barrier was not performed in the No-OOI group and was done in 1 eye in the OOI group \((P = 0.25\) Fisher exact test for all). The OR for OOI status adjusting for RD surgery is similar to OR when not adjusting for RD \((10.8\) vs. \(11.4, P = 0.29)\).

**DISCUSSION**

Epiretinal membrane is a vitreoretinal interface abnormality resulting in a disturbance of macular vision.\(^{21}\) This study demonstrates increased prevalence and incidence of ERM in eyes with inactive extramacular CMV retinitis compared to eyes with no OOI in patients with AIDS. Epiretinal membranes comprise the spectrum of severity from cellophane macular reflex without retinal folds to preretinal macular fibrosis with retinal folds. This may have implication for correlation with visual function, and therefore some studies look at different degrees of ERM separately.\(^{22}\) However, because our outcome measure was not visual function, we did not differentiate between different degrees of ERM, and all degrees were classified as presence of ERM.

The prevalence of ERM in eyes without ocular disease (idiopathic ERM) has been reported to vary with age and among different ethnic groups, with a range of 0.5% to 1.02% in patients younger than 60 years of age and 9.3% in persons 80 years of age and older.\(^{22-24}\) This is consistent with the frequency of ERM at enrollment in our patients without OOI for those given age ranges. Both unadjusted and adjusted prevalence ratios in our group show significantly increased prevalence of ERM in eyes with extramacular CMV retinitis compared to eyes with no OOI. Patient’s age and immune and

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**FIGURE 1.** The LSOCA fundus photography grid outlining the retinal regions into three zones. Zone 1 corresponds to an area of 2 disc diameters (DD) (3600 μm) from the center of macula (green macular circle) and 1 DD (1800 μm) from the margins of the optic disc (green optic disc circle). Zone 2 extends from zone 1 to the vortex veins, and zone 3 extends from zone 2 to the ora serrata.
health status do not seem to contribute to this finding. All eyes with active retinitis had both zones 2 and 3 affected, and the eyes had activity in less than 25% of total retinal area. Therefore, we did not look into correlation of extent of inactive retinitis and the presence of ERM. In one-third of cases the retinitis had active border at baseline, and almost half of the patients had bilateral disease. We have not studied association of CMV retinitis treatments and the presence of ERM, as the HAART regimens were constantly evolving over the years.

A previous study using spectral-domain optical coherence tomography investigated vitreoretinal interface abnormalities at the site of inactive extrafoveal CMV retinitis and adjacent areas. It demonstrated the presence of ERM, vitreoretinal gliosis, and traction in those areas. Our study utilized color fundus photographs and showed that ERM may be present even in the macular area of eyes without an adjacent CMV scar. This expands our knowledge of the distribution of vitreoretinal interface abnormalities in eyes with a history of CMV retinitis. We acknowledge that advanced imaging technology such as optical coherence tomography yields more accurate information on the presence of ERM compared to human evaluation, but this technology has not been a part of LSOCA study. We thus acknowledge that the numbers presented in this report may be slight underestimations of the true prevalence. Another limitation of our study is a survivor bias. Survivor bias in the context of this study means that we cannot evaluate the rate of change in AIDS patients who have died during study follow-up. Even though this is not a population-based study, the strength of our cohort lies in the presence of its own internal control group of HIV-positive patients without OOI, robust sample size from the largest cohort of ocular complications of AIDS in the United States, and protocol-driven data collection at the 5-year interval.

Similar to our prevalence data, the incidence of ERM in eyes with inactive CMV retinitis was statistically significantly higher than in eyes with no OOI as well as higher than reported incidence rates in the literature. In the Blue Mountains Eye Study, the incidence of ERM was reported as 4.4% over 5

**FIGURE 2.** A mosaic image with the LSOCA grid showing an inactive cytomegalovirus (CMV) retinitis lesion in periphery, and epiretinal membrane and tension lines in macular zone 1 area (inset).
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In our study, only four patients underwent cataract surgery during the follow-up period, three of whom were in the No-OOI group. More eyes underwent RD surgery in the OOI group than in the No-OOI group. However, given the nonsignificant difference in ORs for OOI status, the effect of OOI status on prevalence of ERM is not confounded by RD surgery.

Several reports describe the presence of TNF-α in ERM in proliferative vitreoretinopathy and diabetic retinopathy. It is therefore plausible that active infectious retinitis produces cytokines capable of contributing to ERM formation. Similarly, it has been documented that patients with longstanding CMV retinitis who have experienced immune recovery and subsequent uveitis (so-called immune recovery uveitis or IRI) are at increased risk of development of cataract, CME, and ERM. Along with immune-mediated tissue inflammation after recovery of T-lymphocyte counts, there may be additional mechanism(s) causing structural changes in the macula and at the vitreoretinal interface. These may include vitreous changes years. Cataract surgery has been reported to increase the incidence of ERM. In our study, only four patients underwent cataract surgery during the follow-up period, three of whom were in the No-OOI group. More eyes underwent RD surgery in the OOI group than in the No-OOI group. However, given the nonsignificant difference in ORs for OOI status, the effect of OOI status on prevalence of ERM is not confounded by RD surgery.

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Rate) to extend these observations to other causes of infectious visual disturbance and ocular morbidity. It would be insightful presence of ERM. Epiretinal membranes can be a cause of recent onset of OOI is most significant risk factor for the formation compared to what is seen in eyes without OOI. Associated with increased prevalence and incidence of ERM underlying the above findings, however, remains largely during exam. This then predisposes eyes to formation of ERM. Which may be of various severity, subclinical, or not diagnosed during exam. This then predisposes eyes to formation of ERM. Human immunodeficiency virus–associated inflammatory cytokines have been detected also in retinal tissue in noninfectious HIV retinopathy. The exact cellular mechanism underlying the above findings, however, remains largely unknown at this time. In summary, history of extramacular CMV retinitis is associated with increased prevalence and incidence of ERM formation compared to what is seen in eyes without OOI. Recent onset of OOI is most significant risk factor for the presence of ERM. Epiretinal membranes can be a cause of visual disturbance and ocular morbidity. It would be insightful to extend these observations to other causes of infectious retinitis and to immunocompetent populations.

**References**

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APPENDIX

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