Clinical Manifestations of Cytomegalovirus-Associated Posterior Uveitis and Panuveitis in Patients Without Human Immunodeficiency Virus Infection

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Importance: Little attention has been paid to clinical features of cytomegalovirus (CMV) infections in individuals without human immunodeficiency virus (HIV).

Objective: To describe the clinical manifestations and comorbidities of patients without HIV infection who have CMV-associated posterior uveitis or panuveitis.

Design and Setting: Retrospective observational case series in an academic research setting.

Participants: The medical records were reviewed of 18 patients (22 affected eyes) diagnosed as having posterior uveitis or panuveitis who had aqueous positive for CMV by polymerase chain reaction techniques.

Main Outcome Measures: Demographic data, clinical manifestations, and associated systemic diseases were recorded.

Results: Ocular features included focal hemorrhagic retinitis (n = 13) and peripheral retinal necrosis (n = 7). Two eyes had no focal retinal lesions but manifested vasculitis and vitritis. All patients exhibited vitreous inflammation. Inflammatory reactions in anterior segments developed in 14 of 22 eyes (64%). Retinal vasculitis was observed in 16 of 22 eyes (73%) and included mostly arteries (in 13 of 16 eyes [81%]). Eleven of 18 patients were taking immunosuppressive medications (5 for hematologic malignant diseases, 4 for systemic autoimmune diseases, and 2 following organ transplants). One additional patient was diagnosed as having non-Hodgkin lymphoma 3 months after the onset of CMV-associated panuveitis, and another patient had primary immunodeficiency disorder. Of the remaining 5 patients, 2 had diabetes mellitus, and 3 had no associated systemic diseases and exhibited no evidence of immune deficiency.

Conclusions and Relevance: Cytomegalovirus-associated infections of posterior eye segments can develop in patients without HIV infection who have compromised immune function of variable severity but may occur also in individuals who have no evidence of immune insufficiency. Cytomegalovirus infections located in posterior eye segments in patients without HIV infection caused intraocular inflammatory reaction in all cases and demonstrated more variable clinical presentation than classic CMV retinitis observed in patients with HIV infection.


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patients without HIV infection who had uveitis located in the posterior eye segment and report on their clinical manifestations and immune status.

### METHODS

We performed a retrospective review of the medical records of 18 patients without HIV infection who had posterior uveitis or panuveitis and positive polymerase chain reaction (PCR) results of intraocular fluids for CMV from 2 university hospitals (Chiang Mai University Hospital, Chiang Mai [n = 13] and Siriraj Hospital, Bangkok [n = 5]) in Thailand.

Among 170 patients without HIV infection who had uveitis with intraocular fluid analysis, these 18 patients represented all patients from both hospitals without HIV infection who had posterior uveitis or panuveitis and had positive test results for CMV in intraocular fluids (aqueous humor samples in all patients) between January 2006 and December 2011. Patients with HIV infection and patients with anterior uveitis only were excluded from the study.

Samples of intraocular fluid were obtained in patients with uveitis, as well as results of diagnostic screening, which included serologic testing for *Treponema pallidum* and *Toxoplasma gondii* and a chest radiograph. When appropriate, a tuberculin skin test was also administered. Polymerase chain reaction of intraocular fluids for CMV and for human herpesvirus types 1, 2, and 3 was performed on all samples as described previously (herpesvirus type 3 is also known as varicella-zoster virus). Nucleic acid was extracted from 25 μL of intraocular fluid using a commercially available kit (QiAamp DNA Blood Mini Kit; Qiagen, Inc.). Before extraction, 2500 to 5000 copies/mL of phocid herpesvirus type 1 were added to each sample to monitor the quality of extraction and the amplification procedures. Each focal pathogenic DNA was separately analyzed by real-time PCR with a repeated cycling program as previously described. Briefly, 10 μL of the extracted nucleic acid was added to 15 μL of the real-time PCR reaction mixture kit (DyNAamo Probe qPCR; New England Biolabs, Inc.), which contained specific primers and probes. Then, real-time PCR was performed in a detector machine (Chromo4 DNA Engine; Bio-Rad). The lowest detection limits were 3.4 × 10^3 copies/mL for CMV infection, 4.8 × 10^3 copies/mL for human herpesvirus types 1 and 2 infection, 3.5 × 10^3 copies/mL for human herpesvirus type 3 infection, and 4.6 × 10^3 copies/mL for *T. gondii* infection. Included in the study were patients with a positive PCR result for CMV only and negative results for other tested pathogens.

Each patient underwent a full ophthalmic examination, including slitlamp biomicroscopy, tonometry, and indirect ophthalmoscopy. Uveitis was classified according to the anatomical localization as determined by the Standardization of Uveitis Nomenclature (SUN) Working Group. We recorded the demographic data of the patients, their associated systemic diseases, concurrent medication use, and ocular manifestations. This study was performed with the approval of local medical ethics committees. The Fisher exact test was used for statistical analyses. P < .05 was considered statistically significant.

### RESULTS

Our study included 18 patients (22 eyes), with a mean age of 49 years (age range, 29-65 years). There were 11 male patients and 7 female patients (6 with posterior uveitis and 12 with panuveitis). Unilateral involvement was present in 14 patients, and 4 had bilateral involvement, resulting in 22 affected eyes. The mean follow-up time was 24 months (range, 3-60 months).

Eleven of 18 patients were taking immunosuppressive medications; specifically, 2 of the patients had received organ transplants, 4 of the patients had autoimmune connective tissue diseases, and 5 of the patients had hematologic malignant diseases (4 non-Hodgkin lymphoma and 1 acute myeloid leukemia). One additional patient had primary immunodeficiency disorder, and another patient was diagnosed as having non-Hodgkin lymphoma 3 months after the onset of CMV-associated panuveitis (including features of corneal endothelitis, elevated intraocular pressure, and retinal necrotic lesions) (Figure 1A and B, and Table 1). Of the remaining 5 patients, 2 had diabetes mellitus (DM), associated with nonproliferative diabetic retinopathy in both cases, and the other 3 had no systemic diseases or use of medications that could alter their immune system. During the follow-up period, no signs or symptoms of systemic disease or alterations of the immune system were noted (2 patients completed follow-up periods of 2 years, and 1 patient completed a follow-up period of 4 years after the onset of CMV eye infection) (Table 1).

The CD4 cell counts were available in 4 patients (3 with non-Hodgkin lymphoma and 1 with congenital immunodeficiency). The results ranged from 181 to 427 cells/μL.

Clinical features of 22 eyes are given in Table 2 and Table 3. In total, 13 of 22 eyes (59%) had focal hemorrhagic retinal lesions (Figure 1C); 7 of 22 eyes (32%) exhibited peripheral retinal necrosis (3 with hemorrhaging and 4 without hemorrhaging) (Figure 1D and E). Two remaining eyes (9%) had no focal retinal lesions, and both were initially seen with vitritis and retinal vasculitis only (Figure 2A). Areas with indolent granular retinitis were present in 2 eyes (one in combination with retinal necrosis and the other in combination with a focal retinal lesion) (Figure 2B and C).

Retinal vasculitis was present in 16 of 22 eyes (73%), and 13 of 16 (81%) involved the arteries only. Three remaining eyes exhibited (in addition to their retinal lesions) frosted branch angiitis, which predominantly involved veins (Figure 2D and E).

Vitritis was present in 22 of 22 (100%) affected eyes. Anterior segment inflammation was noted in 14 of 22 eyes (64%). One of our patients initially had anterior uveitis with endothelitis and posterior involvement typical of CMV retinitis (Figure 1A and B).

The clinical manifestations did not differ among the various subgroups of our patients (Table 3) but few patients were included in the subgroups. All 5 patients without evident immunosuppression showed unilateral involvement; 1 had a focal retinal lesion, 2 demonstrated peripheral retinal necrosis, and 2 exhibited only vitritis and vasculitis, without other retinal lesions. All 5 manifested severe vitritis, and all had retinal arteritis; anterior chamber inflammatory reactions were present in 4 of 5 eyes. One patient with DM had features of acute retinal necrosis (ARN), and the other patient with DM had a focal necrotic lesion. Three patients who were not taking immunosuppressive medications and who had no DM or other causes or disorders associated with possible immunosuppression were aged 26, 29, and 41 years at the...
onset of their uveitis. Two patients had retinal vasculitis and vitritis and subsequently developed epiretinal membranes with traction.

In general, treatment with systemic (n = 5) and intravitreal (n = 11) ganciclovir sodium had a beneficial effect on inflammatory signs, and the ocular lesions became inactive within 6 to 8 weeks. Immunosuppressive medications were decreased or withdrawn in 4 of 11 patients, none of whom exhibited features consistent with immune reconstitution uveitis (increase in inflammation and development of macular edema). During the follow-up period, retinal detachment developed only in 1 eye of a patient with non-Hodgkin lymphoma and ocular features of ARN, which had an incidence of 3% per person per eye-year (1 case in 30.4 person eye-years). Pars plana vitrectomy was performed in patients with epiretinal membranes and traction (2 eyes) or retinal detachment (1 eye).

**COMMENT**

Our results document that posterior uveitis and panuveitis due to CMV can develop in patients without HIV infection who have moderate or slight degrees of immnosuppression, as well as in occasional patients without.
any evidence of immunosuppression, during several follow-up years. Furthermore, we showed that all patients without HIV infection who had posterior segment involvement due to CMV exhibited associated inflammation in the vitreous and that 14 of 22 affected eyes (64%) developed an inflammatory reaction in the anterior chamber (Table 1). The presence of retinal vasculitis was a common characteristic (occurring in 16 of 22 eyes [73%]), predominantly involving arteries. The retinal features resembled in part the typical manifestations of CMV retinitis found in patients with HIV infection, described as hemorrhagic and granular types of retinitis, but our cases also included manifestations typical of ARN, as well as cases with retinal vasculitis associated with vitritis.

Cytomegalovirus is a ubiquitous member of the family of human herpesvirus types 1 and 2, and the seroprevalence of CMV is about 90% among the Thai adult population.23 Cytomegalovirus retinitis can occur in patients who have deficient T-cell responses against the CMV (usually due to the HIV infection or to the immunosuppressive medication), and the prevalence of CMV retinitis has been linked to the degree of immunosuppression.24 Systemic CMV infection in patients with a healthy immune system has often been reported to be subclinical, while ocular involvement during viremia has not been regularly documented. However, a 2008 review of severe systemic CMV infection among 290 immunocompetent adults demonstrated that the most frequent sites

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Immunosuppressive Medication Use at the Onset of CMV-Associated Uveitis</th>
<th>Comorbidity</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/42</td>
<td>None</td>
<td>Primary immunodeficiency disorder</td>
<td></td>
</tr>
</tbody>
</table>
| 2/M/64                 | None                                            | Diabetes mellitus | Glycated hemoglobin, 10.0%  
| 3/F/50                 | None                                            | Diabetes mellitus | Glycated hemoglobin, 9.9%  
| 4/F/49                 | None                                            | Diagnosis of non-Hodgkin lymphoma 3 mo after onset of CMV-associated uveitis |  
| 5/M/50                 | None                                            | Non-Hodgkin lymphoma | Completed 2 cycles of chemotherapy 2 mo before the onset of CMV-associated uveitisa  
| 6/M/61                 | None                                            | Non-Hodgkin lymphoma | Completed 5 cycles of chemotherapy 2 mo before the onset of CMV-associated uveitisa  
| 7/M/65                 | None                                            | Non-Hodgkin lymphoma | Completed 8 cycles of chemotherapy 4 mo before the onset of CMV-associated uveitisa  
| 8/F/59                 | None                                            | Non-Hodgkin lymphoma | Completed 8 cycles of chemotherapy 9 mo before the onset of CMV-associated uveitisa  
| 9/F/52                 | None                                            | Acute myeloid leukemia | Completed 8 cycles of chemotherapy 5 mo before the onset of CMV-associated uveitisb  
| 10/M/54                | Tracrolimus (6 mg/d)                            | Renal transplant |  
| 11/F/58                | Cyclosporine (150 mg/d)                         | Renal transplant |  
| 12/F/45                | Prednisolone (40 mg/d), azathioprine (100 mg/d) | Myasthenia gravis and transverse myelitis | Died 1 mo after the onset of CMV-associated uveitis  
| 13/M/59                | Prednisolone (10 mg/d), cyclophosphamide (50 mg/d) | Nephritis |  
| 14/F/39                | Prednisolone (10 mg/d), cyclophosphamide (25 mg/d) | Systemic lupus erythematosus |  
| 15/M/45                | Prednisolone (40 mg/d)                          | Idiopathic thromboocytopenic purpura |  
| 16/M/29                | None                                            | None | No evidence of disorder associated with immune deficiency during a 2-y follow-up period  
| 17/M/26                | None                                            | None | No evidence of disorder associated with immune deficiency during a 2-y follow-up period  
| 18/M/41                | None                                            | None | No evidence of disorder associated with immune deficiency during a 2-y follow-up period  

Abbreviation: Ellipsis, not applicable.
a Non-Hodgkin lymphoma chemotherapy included a combination of rituximab, vincristine sulfate, cyclophosphamide, and prednisolone.
b Acute myeloid leukemia chemotherapy included a combination of fludarabine phosphate, idarubicin hydrochloride, and cytosine arabinoside.

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Affected Eyes, No. (%) (N = 22)</th>
</tr>
</thead>
</table>
| Fine keratic precipitates | 8 (36)  
| Endothelitis | 1 (5)  
| Anterior chamber cells | 14 (64)  
| Posterior synechiae | 2 (9)  
| Focal hemorrhagic retinitis | 13 (59)  
| Granular retinitis | 2 (9)  
| Acute retinal necrosis | 7 (32)  
| No focal retinal lesions, only vasculitis and vitritis | 2 (9)  
| Retinal arteritis | 13 (59)  
| Frosted branch angiitisa | 3 (14)  
| Vitritis | 22 (100)  
| Intraocular pressure >24 mm Hg | 3 (14)  

a One eye in combination with focal retinitis and another eye in combination with retinal peripheral necrosis.
of severe CMV infection in these patients were the gastrointestinal tract and the central nervous systems; eye involvement was also noted.\textsuperscript{23} That series included 16 patients with all types of eye involvement, including conjunctivitis and anterior and posterior eye segment inflammation.

The largest study of patients without HIV infection who had CMV retinitis, published by Kuo et al\textsuperscript{6} in 2004, included 18 patients with profound immunosuppression diagnosed as having CMV retinitis on clinical grounds only. In that study, the rates of mortality, vision loss, and immune reconstitution uveitis were found to be similar to those of patients with HIV infection and CMV retinitis receiving HAART. Immune reconstitution uveitis occurred in 4 of 18 patients (incidence of 13% per person-year); however, the number of patients in whom immunosuppressive treatment could be decreased or withdrawn was not given. These results contrast with those of our series, which included patients with less severe or the absence of immunosuppression. In our study, immunosuppressive treatment was decreased or withdrawn in 4 of 11 patients, but none developed features of immune reconstitution uveitis during the follow-up period. Intraocular inflammation was present in all of our patients with CMV, in contrast to the series by Kuo et al.\textsuperscript{6} Moreover, the mortality in their study was high (23% per person-year vs 3% per person-year in our series). These discrepancies can be explained by different inclusion criteria and by more severe immunosuppression among patients in the earlier study. The incidence rate of retinal detachment found previously among patients without HIV infection who had CMV retinitis is similar to our results (3.7% vs 3% per eye-year), which is lower than the incidence rates among patients who have HIV and CMV retinitis (22% with HAART and 44% without HAART).\textsuperscript{5,20}

Ocular manifestations of CMV infection in hosts with HIV infection have been extensively reported.\textsuperscript{2,26,31} However, systematic studies\textsuperscript{3,6} on the clinical manifestations of CMV infection in posterior eye segments among patients without HIV infection are rare.

The clinical manifestations of HIV-associated CMV retinitis include the classic features of necrotizing retinitis, with variable degrees of hemorrhaging (“cottage cheese with ketchup” or “pizza pie” retinopathy), as well as a granular form of retinitis that is sometimes in combination with frosted branch angiitis; associated inflammatory signs are lacking.\textsuperscript{27-31} In contrast to clear media observed by Kuo et al,\textsuperscript{6} all of our patients demonstrated associated vitritis, and more than half had concurrent anterior uveitis, while the absence of intraocular inflammation in patients with HIV infection and CMV retinitis is typical.\textsuperscript{27-31} Our findings clearly show that the characteristics of posterior segment involvement caused by CMV in patients without HIV infection represent a much wider spectrum of clinical manifestations, which include frequent prevalence of retinal arteritis, variable signs of intraocular inflammation, and the presence of retinal involvement, varying from focal lesions to extended ARN. Seven of our patients without HIV infection who had CMV exhibited clinical characteristics of ARN. The prevalence of the clinical syndrome of ARN among individuals with HIV infection varies between 0.4% and 1.1%,\textsuperscript{2,32} which is much lower than that in our series. Acute retinal necrosis is mostly associated with human herpesvirus types 1, 2, and 3, but occasional CMV cases have been reported.\textsuperscript{33} The presence of ARN due to CMV has been reported in a patient without HIV infection who had DM.\textsuperscript{34}

The retinal vessels may have an important role in the pathogenesis of CMV retinitis. Clinically, the areas of CMV retinitis are located along the retinal vessels, and immunohistochemical studies\textsuperscript{35,36} have revealed the presence of CMV proteins in the retinal vascular endothelium in the areas adjacent to retinal necrosis. It has been proposed that CMV infection in the retina initially occurs in the vascular endothelium. The association of HIV vasculopathy and subsequent retinitis has been reported.\textsuperscript{37}

### Table 3. Clinical Manifestations of Cytomegalovirus (CMV)–Associated Posterior Uveitis or Panuveitis in Patients With vs Without Immunosuppression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Eyes in Patients With Immunosuppression (n = 17)</th>
<th>Eyes in Patients Without Immunosuppression (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Organ Transplantation</td>
<td>Hematologic Malignancy</td>
</tr>
<tr>
<td>Focal retinal lesions</td>
<td>2 (67)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Peripheral retinal necrosis</td>
<td>1 (33)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Retinal vasculitis</td>
<td>3 (100)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Retinal hemorrhaging</td>
<td>3 (100)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>1 (33)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Vitritis</td>
<td>3 (100)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Intraocular pressure &gt;24 mm Hg</td>
<td>0</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Visual acuity at the onset of CMV–associated uveitis &lt;0.1</td>
<td>1 (33)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Ratio of Unilateral to Bilateral Involvement</td>
<td>1:1</td>
<td>5:1</td>
</tr>
<tr>
<td>Organ Transplantation</td>
<td>1 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Hematologic Malignancy</td>
<td>1 (33)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Autoimmune Disease</td>
<td>1 (33)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Primary Immunodeficiency Disorder</td>
<td>1 (33)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>No Abnormality Except Ocular Disease</td>
<td>1 (33)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1 (33)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>P Value</td>
<td>.06</td>
<td>.52</td>
</tr>
</tbody>
</table>
In our series, a high prevalence of vascular involvement among patients without HIV infection who had CMV infection was noted, and 2 patients without necrotic retinal changes manifested severe vasculitis only. Involvement of retinal vessels is common in CMV retinitis and can affect arteries and veins. The exact role of HIV vasculopathy in the development of CMV retinitis among patients with HIV infection is controversial. Predominant involvement of retinal veins among individuals with HIV infection and CMV retinitis has been noted and consisted primarily of perivenous sheathing. In contrast, we observed primary involvement of retinal arterioles in our patients without HIV infection who had CMV and posterior uveitis. The predominance of retinal arteritis was also noted in ARN associated with human herpesvirus types 1, 2, or 3 infection. It may be that retinal necrosis due to viral infections (including CMV) in patients without HIV infection is frequently associated with involvement of retinal arteries. The severe loss of immunity in patients with HIV infection might explain the absence of arteritis even in the presence of retinal necrotic lesions. A severe retinal vasculitis, frosted branch angiitis may be associated with multiple infective agents, including CMV. Frosted branch angiitis was ob-

Figure 2. Clinical presentation of cytomegalovirus-associated posterior uveitis and panuveitis in patients 5, 8, and 18 in Table 1. A, A 41-year-old healthy man (patient 18) without evidence of previous immunosuppression was seen with severe unilateral vitritis complicated by epiretinal membrane formation and retinal traction. After pars plana vitrectomy, severe vasculitis and sheathing became visible, but retinal lesions were not observed. B and C, A 59-year-old woman (patient 8) with non-Hodgkin lymphoma had been successfully treated with chemotherapy. She developed cytomegalovirus-associated unilateral peripheral retinal necrosis, areas of granular retinitis, and retinal arteritis 16 months after the diagnosis of non-Hodgkin lymphoma. D and E, A 50-year-old man (patient 5) with underlying non-Hodgkin lymphoma had been receiving repeated cycles of chemotherapy. He developed cytomegalovirus-associated panuveitis with focal retinitis and peripheral retinal necrosis, as well as frosted branch angiitis.
erved in our series in 3 of 22 eyes (14%) and was always associated with the presence of retinitis.

In our series, 2 of 5 patients (both with nonproliferative diabetic retinopathy) who were not receiving immunosuppressive medications had DM. Notably, 2 patients without HIV infection who had DM have been previously reported as having PCR-proved CMV-associated panuveitis and exhibited multiple keratic precipitates, vitreous opacities, necrotic retinal lesions, and arterial sheathing. Some research has suggested that CMV infection might be associated with DM and its complications. In vitro studies of the immune cells of patients with DM have demonstrated significant defects that bear similarity to abnormalities described in immunodeficiency syndromes and that were hypothetically related to the frequent and chronic development of infections among individuals with DM. However, it might also be feasible that vasculopathy present in DM may have an important role in the development of CMV infection among individuals with DM.

The CMV-induced focal retinitis in our series was frequently associated with hemorrhaging, and no eyes showed associated pigmented scars, which might help to differentiate these lesions from ocular toxoplasmosis. Two of our patients without evident immune system abnormalities had no necrotic retinal lesions and were initially seen with vitritis and vasculitis only (manifesting in both arteries and veins), which indicates the possibility of CMV involvement in the pathogenesis of retinal vasculitis in immunocompetent patients.

Cytomegalovirus-associated anterior uveitis represents a distinct clinical entity that occurs in immunocompetent patients and has been reported mainly in Asia, but sporadic cases from Europe have also been described. The exact pathogenesis of CMV-associated anterior uveitis and its association with primary systemic infection remain unknown. Some of the typical manifestations of this entity, such as endothelitis and high intraocular pressure, were also observed in the anterior segments of our patients.

The retrospective nature of our study precludes any conclusions about the prevalence of CMV infection in posterior eye segment inflammation. The limited number of patients included in our study prevents a full depiction of clinical signs associated with CMV infection in patients without HIV infection.

In conclusion, CMV-associated infection of posterior eye segments can develop in patients without HIV infection who have variable degrees of compromised immune function but may also occur in individuals who have no evidence of immune insufficiency. Clinical features of CMV-associated posterior segment eye infection in patients without HIV infection might differ from those of patients with HIV infection and typically include signs of intraocular inflammation and the presence of vasculitis, with the frequent involvement of arteries. Retinal necrotic lesions are often (but not always) present, and 7 of our patients without HIV infection who had CMV infection in posterior eye segments exhibited typical features of ARN. It may be that CMV infection located in posterior eye segments of patients without HIV infection is more frequent and has more variable clinical presentation than previously thought.

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Author Contributions: Dr Pathanapitoon had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest Disclosures: None reported.

REFERENCES


