Immune Recovery Vitritis Associated With Inactive Cytomegalovirus Retinitis

A New Syndrome

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Objective: To describe a syndrome of posterior segment intraocular inflammation that causes visual loss in patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. This syndrome was associated with immune recovery mediated by combination antiretroviral treatment including protease inhibitors.

Design: A case-control study at 2 university medical centers.

Participants: One hundred thirty patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis were examined at 2 medical centers for 15 months. In addition, the medical records of 509 patients examined at 1 center for 11 years before the initiation of protease inhibitor therapy were analyzed retrospectively.

Results: Five patients with symptomatic vitritis and papillitis with cystoid macular edema or epiretinal membrane formation were documented. In each patient there was inactive cytomegalovirus retinitis that had not caused visual decrease before the onset of inflammation. All patients had elevated CD4+ T lymphocyte levels (median increase, 86×10^6/L [86 cells/mm^3]) after combination treatment including protease inhibitors. Two patients with cystoid macular edema were treated with corticosteroids and had resolution of the cystoid macular edema and an increase in visual acuity without reactivation of the retinitis. Retrospective analysis failed to disclose similar patients with intraocular inflammation in the era before the introduction of protease inhibitors.

Conclusions: This newly described syndrome of posterior segment inflammation related to cytomegalovirus retinitis is a cause of visual morbidity in patients with acquired immunodeficiency syndrome. It is associated with increased immune competence as a result of combined antiretroviral treatment with protease inhibitors and may be amenable to corticosteroid therapy without reactivation of retinitis.


The introduction of human immunodeficiency virus (HIV)–specific protease inhibitors in the treatment of acquired immunodeficiency syndrome (AIDS) has resulted in a significant improvement in immune status in many patients, as indicated by increased levels of CD4+ T lymphocytes and decreased levels of plasma HIV messenger RNA.1,2 The 4 protease inhibitors currently available are ritonavir, indinavir sulfate, nelfinavir mesylate, and saquinavir sulfate. All 4 competitively inhibit the protease-mediated cleavage of viral polyproteins, preventing the maturation of infectious virions. The result is inhibition of HIV replication.

Cytomegalovirus (CMV) retinitis in patients with AIDS is associated with profound immunodeficiency and a CD4+ T lymphocyte count below 100×10^6/L (100 cells/mm^3; usually <50×10^6/L [<50 cells/mm^3]).3-5 It is typically characterized by necrotizing retinitis with little or no intraocular inflammatory response, even in the presence of extensive retinal involvement.

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Macular inflammation or exudation in patients with CMV retinitis is uncommon. Serous macular exudation associated with posterior active CMV retinitis in patients with AIDS has been described by Gangan et al.6 Palestine and Frishberg7 described a patient with AIDS-related macular edema with cotton-wool spots, other microvascular abnormalities, and, eventually, a macular star, which was attributed to HIV microvasculopathic complications. A patient with cystoid macular edema (CME) associated with AIDS and
PATIENTS AND METHODS

After the introduction of HIV-specific protease inhibitors for the treatment of patients with AIDS, we examined several patients with decreased visual acuity due to posterior segment inflammatory complications and inactive CMV retinitis. According to the grading system (1-4) proposed by Nussenblatt et al.12 In addition, the levels of CD4+ T lymphocytes and plasma viral HIV messenger RNA were checked every 2 to 3 months as indicated to monitor antiretroviral therapy.

To evaluate the role of protease inhibitor therapy in the occurrence of inflammatory complications, an additional computer search was performed at the AORU using the database of CMV retinitis patients from January 1986 to December 1995, before the introduction of highly active antiretroviral treatment (HAART) at this institution.

We also evaluated 2 control groups from the AORU database for incidence of intraocular inflammation as follows: (1) HIV-positive patients without a history of CMV retinitis who were receiving HAART and had elevated CD4+ T lymphocyte counts (CD4+ T lymphocyte count, \(\geq 50 \times 10^6/L \geq 50 \text{ cells/mm}^3\); n = 31) and (2) HIV-positive patients with a history of CMV retinitis who were receiving HAART but whose CD4+ T lymphocyte counts remained low (CD4+ T lymphocyte count, \(\leq 30 \times 10^6/L \leq 30 \text{ cells/mm}^3\); n = 29).

At the Cleveland Clinic, all patients of a single physician (C.Y.L.) were analyzed retrospectively during the same period. Participation was voluntary, and we received informed consent from all patients.

CMV retinitis was described by Weinberg and Moor- thy.9 This patient developed anteroposterior segment intraocular inflammation with CME. He was in a severely immunosuppressed condition (CD4+ T lymphocyte count, \(3 \times 10^6/L \leq 3 \text{ cells/mm}^3\)) and was not being treated with protease inhibitors. However, he was treated concomitantly with rifabutin, which may have been the cause of the inflammation. This is, to the best of our knowledge, the only documented patient with inflammatory CME related to AIDS with severe immunodeficiency. It has been postulated that the profound immunodeficiency in patients with AIDS has a protective effect against CME and against other vision-threatening inflammation-induced complications of necrotizing retinitis, such as papillitis and epiretinal membrane formation.6

We evaluated 5 patients undergoing treatment with protease inhibitors who had rising CD4+ T lymphocyte levels and inactive CMV retinitis. All demonstrated moderate vitritis and papillitis, some with CME. We attribute these inflammation-induced complications to the increased immunocompetence of these patients. We term this new syndrome immune recovery vitritis.

REPORT OF CASES

CASE 1

A 43-year-old man (patient 4 in Table 1 and Table 2) in whom HIV infection was diagnosed in January 1989 was diagnosed as having AIDS in March 1994 when he developed Pneumocystis carinii pneumonia. The patient developed CMV colitis in April 1996 and was treated with intravenous ganciclovir. He was receiving zidovudine and lamivudine at the time. Treatment with a protease inhibitor (indinavir) was initiated in June 1996. In October 1996, while receiving maintenance intravenous ganciclovir therapy, he presented at another institution for ophthalmic evaluation and was found to have clinically inactive CMV retinitis of the left eye. In December 1996, on initial examination at the AORU, the patient complained of blurring of vision and floaters in the left eye. Visual acuity was 20/25 OD and 20/63 OS. Ophthalmoscopic examination results disclosed inactive CMV retinitis in the nasal periphery (4.0 disc diameters from the center of the fovea) of the left eye with moderate vitritis (+2) and CME. The border of the retinitis showed no opacity and appeared completely healed. There was no anterior segment inflammation. The right eye was healthy. The CD4+ T lymphocyte count was \(108 \times 10^6/L \leq 108 \text{ cells/mm}^3\). Fluorescein angiography was performed, and results showed moderate leakage in a petaloid pattern consistent with CME, with mild leakage from the optic disc (Figure 1).

A posterior subtenon injection of repository methylprednisolone (80 mg) was administered on January 10, 1997, and the patient continued maintenance therapy with ganciclovir. Another injection was given 8 weeks later and resulted in partial resolution of the CME ophthalmoscopically 2 weeks after the second injection. Visual acuity improved to 20/40 OU. Cytomegalovirus retinitis remained inactive.

CASE 2

A 32-year-old man (patient 3 in Tables 1 and 2) was diagnosed as having AIDS 34 months after being diagnosed as having HIV infection. Cytomegalovirus retinitis of the right eye was diagnosed in December 1994 and was treated with ganciclovir followed by combination ganciclovir and foscarnet after reactivation of the retinitis during ganciclovir therapy. Highly active antiretroviral treatment with a protease inhibitor (ritonavir initially, then indinavir) was initiated in January 1996, and elevation of the CD4+ T lymphocyte count occurred 3 months later \((22-63 \times 10^6/L \leq 22-63 \text{ cells/mm}^3\)) and the patient con-
continued therapy with combination ganciclovir and foscarnet. Posterior segment intraocular inflammation manifested initially as moderate vitritis (2+) with floaters. The patient developed CME and papillitis with a decrease in visual acuity (20/40 OD), as documented by indirect ophthalmoscopy, fundus photography, and fluorescein angiography. Cytomegalovirus retinitis was inactive clinically for 9 months at the onset of CME.

Posterior segment inflammation was treated with systemic corticosteroids (60 mg of prednisone for 2 weeks, decreased by 20 mg every 2 weeks). The CME improved clinically as shown by fluorescein angiography. Visual acuity improved to 20/30 OD. Cytomegalovirus retinitis did not reactivate after corticosteroid treatment.

CASE 3

A 44-year-old man (patient 5 in Tables 1 and 2) was diagnosed as having AIDS in February 1995 with the diagnosis of Kaposi sarcoma. The patient was diagnosed at another institution as having CMV retinitis of the right eye in December 1995 and was treated with an induction dose of intravenous ganciclovir followed by oral ganciclovir therapy for maintenance. The retinitis reactivated in March 1996 and again in June 1996, and the patient was reinduced. Treatment with a protease inhibitor (indinavir) was initiated in September 1996. In October 1996, on initial examination at the AORU, the patient had no visual complaints. Visual acuity was 20/25 OD and 20/15 OS. There was active CMV retinitis of the superior midperiphery (3.5 disc diameters from the center of the fovea) of the right eye without anterior segment inflammation. The left eye was normal. The patient received a single intravitreal injection of cidofovir (15 µg), and oral maintenance ganciclovir therapy was continued. There was no iritis or hypotony after the injection. Resolution of the retinitis was noted 4 weeks after the injection, and retinitis remained inactive through the most recent examination. In November 1996, oral ganciclovir therapy was discontinued, and

Table 1. Medical Data in Patients With Immune Recovery Vitritis*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Date of Diagnosis</th>
<th>Antiretroviral Treatment</th>
<th>Anti-CMV Treatment</th>
<th>CD4+ Cell Count at CMV Diagnosis, ×10⁹/L: Date</th>
<th>Plasma HIV mRNA at Onset of Inflammation</th>
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<tr>
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<td>12/92</td>
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<td>PCP: 1/93</td>
<td>Ganciclovir</td>
<td>Indinavir: 12/12/95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fungal: 3/93</td>
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<td>6/4/96</td>
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<td>2</td>
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<td>3/26/96</td>
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<td>Ganciclovir</td>
<td>Ritonavir: 1/15/96</td>
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<tr>
<td>4</td>
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<td>3/15/95</td>
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<td>Zidovudine Lamivudine</td>
<td>Indinavir: 9/27/96</td>
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<tr>
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<td>2/15/95</td>
<td>None</td>
<td>Ganciclovir</td>
<td>Indinavir: 9/30/96</td>
</tr>
</tbody>
</table>

* HIV indicates human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; mRNA, messenger RNA; PCP, Pneumocystis carinii pneumonia, and VZV, varicella-zoster virus.

Table 2. Ocular Findings in Patients With Immune Recovery Vitritis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Iritis: Date</th>
<th>Vitritis: Date</th>
<th>Macular Changes: Date</th>
<th>Visual Acuity</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1+ cells: 8/6/95</td>
<td>2-3+ cells: 7/30/96</td>
<td>ERM: 10/22/96</td>
<td>20/25</td>
<td>20/80</td>
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<tr>
<td>2</td>
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<td>Cystoid macular edema: 9/13/96</td>
<td>20/20</td>
<td>20/80: 16</td>
</tr>
<tr>
<td>3</td>
<td>1+ cells: 3/15/96</td>
<td>2+ cells: 3/15/96</td>
<td>Macular edema: 12/15/96</td>
<td>20/20</td>
<td>20/40: 10</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>2+ cells: 12/10/96</td>
<td>Cystoid macular edema: 12/10/96</td>
<td>20/20</td>
<td>20/63: 23</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>2-3+ cells: 1/3/97</td>
<td>ERM: 1/17/97</td>
<td>20/25</td>
<td>20/40</td>
</tr>
</tbody>
</table>

* Weeks of decreased vision before therapy or before spontaneous vision recovery. ERM indicates epiretinal membrane.
The patient was followed up for reactivation of retinitis. The CD4+ T lymphocyte count was $59 \times 10^6/L$ (59 cells/mm$^3$). In January 1996, 4 months after the initiation of protease inhibitor therapy, the patient complained of floaters and blurring of vision in the right eye. Visual acuity had decreased to 20/32 OD. On examination, CMV retinitis remained inactive, and there was 2 vitritis. On January 17, 1997, the patient complained of increasing blurring of vision in the affected eye. The visual acuity was 20/40 OD and funduscopy disclosed 2 vitritis and macular changes consistent with epiretinal membrane and diffuse macular edema, and the retinitis remained inactive. Results of fluorescein angiography showed diffuse leakage of fluorescein in the macula, with mild leakage from the optic disc (Figure 2). The CD4+ T lymphocyte count was $79 \times 10^6/L$ (79 cells/mm$^3$). The epiretinal membrane has not been treated surgically.

At the AORU between December 1995 and March 1997, 108 patients (174 eyes) with AIDS and CMV retinitis were examined, 66 of whom had bilateral and 42 of whom had unilateral disease. During the study period, 102 of the 108 patients received protease inhibitors. Four (3.7%) of 108 patients and 4 (2.3%) of 174 eyes had significant posterior segment intraocular inflammation. At the Cleveland Clinic during the same period, 22 patients with AIDS-related CMV retinitis were evaluated, 7 of whom received protease inhibitors. One patient developed posterior segment inflammation. All of these 5 patients (5 eyes) had moderate-to-severe vitritis (2-3 on a 1-4 scale) and papillitis; 3 developed CME and the other 2 developed epiretinal membranes. The patients included 4 men and 1 woman whose ages ranged from 31 to 48 years (median, 43 years). The diagnosis of AIDS preceded the di-
agnosis of CMV retinitis by a median of 17.5 months (range, 7-36 months) in 4 patients, and CMV retinitis was the AIDS-defining diagnosis in the other patient.

All 5 patients were initially treated for CMV retinitis with ganciclovir sodium (induction dosage, 10 mg/kg per day; maintenance dosage, 5 mg/kg per day) or combination ganciclovir and foscarnet sodium. Two patients received a single intravitreal injection of cidofovir (15 µg). This therapy was not associated with iritis in either patient and preceded the onset of posterior segment inflammation by 3 months in patient 5 and 1 month in patient 2. The inflammatory complications in these patients, therefore, were not attributed to cidofovir therapy.13

One patient was treated with intravenous cidofovir, which was initiated 2 months after the onset of posterior segment intraocular inflammation with CME and therefore was not implicated in causing the inflammation.

All of the medications that the patients were receiving were reviewed (Table 3), and medications known to cause intraocular inflammation were not included. None of the patients were receiving treatment with rifabutin within 2 months of the onset of vitritis.

Between December 1995 and June 1996, before the onset of uveitis, all 5 patients initiated HAART with a combination of 1 or 2 reverse transcriptase inhibitors (lamivudine, zidovudine, or stavudine) and 1 protease inhibitor (indinavir or ritonavir). As a result of this treatment, all patients experienced a marked increase in CD4+ T lymphocyte levels (range of increase, 41-283×10^3/µL [41-283 cells/mm^3]; mean increase, 130×10^3/µL [130 cells/mm^3]; median increase, 86×10^3/µL [86 cells/mm^3]) and a reduction of plasma HIV messenger RNA to undetectable levels. The time between the initiation of HAART and the elevation of CD4+ T lymphocyte levels was 2 to 5 months (median, 2 months).

Posterior segment inflammatory complications manifested as a painless decrease in visual acuity (20/40-20/63) and floaters, which occurred 2 to 16 weeks (median, 4 weeks) after the elevation of CD4+ T lymphocyte counts. At the onset of posterior segment inflammation, all of the patients had inactive CMV retinitis in zones 1 or 22,14 that had not caused visual inflammation, all of the patients had inactive CMV retinitis, as evaluated at 2 institutions between December 1995 and March 1997. All of these patients had marked increases in CD4+ T lymphocyte levels (63-300×10^3/µL [63-300 cells/mm^3]; mean, 173×10^3/µL [173 cells/mm^3]); mean, 130×10^3/µL [130 cells/mm^3]); median increase, 86×10^3/µL [86 cells/mm^3]) and a reduction of plasma HIV messenger RNA to undetectable levels. The time between the initiation of HAART and the elevation of CD4+ T lymphocyte levels was 2 to 5 months (median, 2 months).

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To determine whether a similar entity existed before the advent and use of protease inhibitors, we reviewed the medical records of all of the patients examined at the AORU between August 1986 and December 1995, before the initiation of HAART at this institution. The records revealed 509 patients (830 eyes) with AIDS-related posterior segment ocular disease during this period. Review of these records failed to identify any patients with 2 to 3+ vitritis related to CMV retinitis. Papillitis was found in 8 eyes, 2 of which were not associated with CMV retinitis but were related to syphilis. In the remaining 6 eyes (0.1%) there was involvement of the peripapillary retina with active CMV retinitis. This was not the case with any of the patients of the present series. Three patients with CME were documented, but these were not related to CMV retinitis; 1 was a patient with endogenous endophthalmitis and the other 2 were patients with retinitis. Thirty-two patients (35 eyes) with severe macular exudation related to active CMV retinitis were documented, as described by Gangan et al.6 These patients manifested neurosensory retinal detachments with lipid exudates rather than CME. Finally, this review revealed 3 patients (3 eyes, 0.4%) with epiretinal membranes. All of these were related to CMV retinitis of an area of the retina adjacent to the membrane and were not associated with significant intraocular inflammation. In the patients in the present report there was no CMV retinitis adjacent to the fovea.

Regarding the 2 control groups outlined in the “Patients and Methods” section, we found no incidence of intraocular inflammation in any patient from either control group: those without CMV retinitis with elevated CD4+ counts (0 of 31) or those with CMV retinitis with low CD4+ counts (0 of 29).

We describe 5 patients with clinically significant posterior segment intraocular inflammation associated with AIDS and inactive CMV retinitis, as evaluated at 2 institutions between December 1995 and March 1997. All of these patients had marked increases in CD4+ T lymphocyte levels (63-300×10^3/µL [63-300 cells/mm^3]); mean,
Yotomegalovirus retinitis in patients with AIDS typically manifests as a progressive necrotizing retinitis with little or no intraocular inflammation. Vitritis is not uncommon, but, when present, it is mild and minimally symptomatic, unlike that seen in our patients, who were very symptomatic. Macular inflammation or exudation is rare and has been associated with diffuse macular edema confirmed by fluorescein angiography. Of the 3 patients with CME, 2 were treated with corticosteroids. One of these 2 patients received oral prednisone, and the other patient was treated with periocular repository corticosteroid injections. In the first case, the patient’s internist believed that oral corticosteroid treatment would be safe (short courses of systemic corticosteroids are routinely given to patients with AIDS with P carinii pneumonia). In addition, administration of oral corticosteroids can be rapidly discontinued in the event of reactivation of CMV retinitis. The result, in both patients, was resolution of the CME with an increase in visual acuity and without reactivation of CMV retinitis. The patients with epiretinal membranes have not undergone surgery. Cytomegalovirus retinitis did not involve the macula or papillomacular bundle in any of these patients, and visual acuity was unaffected before the onset of posterior segment inflammation. Furthermore, corticosteroid therapy resulted in visual improvement in the 2 patients who were treated. We conclude, therefore, that the visual loss in these patients was the result of intraocular inflammation.

Cytomegalovirus retinitis in patients with AIDS microvasculopathy7 or active CMV retinitis is mild and minimally symptomatic, unlike that seen in patients with AIDS. The posterior segment inflammatory responses seen in our series could therefore be attributed to increased immune function as a result of HAART including protease inhibitors and cytokine reconstitution associated with the presence of inactive CMV retinitis, combination antiretroviral therapy with protease inhibitors, and evidence of at least partial immune reconstitution suggested by elevated CD4+ cell counts. However,
there are many patients with all 3 factors who do not develop inflammation. The reason is not known. The inflammatory reaction could be in response to CMV antigens expressed on cells that have been latently infected, near the areas of previously active CMV retinitis. Indeed, the immune response to CMV antigens varies in patients with AIDS. Schirer et al. previously have shown that this may be related to the predisposition to CMV retinitis. The heterogeneity of the T-lymphocyte response has already been documented. Further studies are necessary to evaluate the incidence and pathogenesis of this newly described syndrome.

Immune recovery vitritis emerges as a new syndrome and a cause of visual morbidity in patients with AIDS. It is associated with improving immune status as a result of HAART and may be reversible with corticosteroid treatment without reactivation of CMV retinitis.

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REFERENCES


