Management of Cytomegalovirus Retinitis in a Patient with AIDS and Poor Compliance with HAART Therapy

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Abstract

Cytomegalovirus retinitis (CMVR) is a common ocular condition in severely immunocompromised HIV patients. This report follows the diagnosis and treatment of CMVR in an asymptomatic male with a CD4+ count below 50 cells/ul.

Key Words: Cytomegalovirus Retinitis (CMVR), Acquired Immune Deficiency (AIDS), Ganciclovir
Case Report

A 50 year old African American male presented on April 29, 2010 with a chief complaint of near blur, occasional redness and tearing with no ocular pain in both eyes (OU). His medical history was significant for anemia, cocaine abuse and HIV. His last CD4+ count was 51 cells/ul, improved from 25 cells/ul two months prior. His last viral load measured 82,060. His medications included Azythromycin, Hydroxyzine Pamoate, Doxepin, Megestrol, Chlorhexidine, Bactrim, Nevirapine, Nystatin, Truvada and a Multivitamin. His ocular history was unremarkable.

His best corrected visual acuity was 20/20 in the right eye (OD) and left eye (OS) at distance and near. Extra ocular motility, confrontation visual fields and pupils were all within normal limits. Anterior segment exam revealed mild punctate epithelial erosions, reduced tear break up time and mildly capped meibomian glands OD, OS. Ophthalmoscopy revealed two cotton wool spots OD and two cotton wool spots OS with one blot hemorrhage OS (see photo A and B). There were no signs of infection, with no anterior chamber or vitreous cells. All other exam findings were within normal limits. The patient was diagnosed as having HIV/AIDSs with mild retinopathy OD, OS along with dry eye syndrome and meibomian gland dysfunction OU. The patient was started on artificial tears and warm compresses and educated to return to clinic in three to four months for a dilated fundus exam or sooner if any changes in vision.

Photos A and B- photo on the left is right eye at initial presentation, photo on the right is left eye at initial presentation.

Follow Up #1

Four months later on August 13, 2010, the patient returned for scheduled follow up with no new ocular complaints. His last CD4+ T-lymphocyte count had improved to 90 cells/ul and the viral load was less than 15,000. Best corrected visual acuity remained 20/20 OD, OS at distance and near. Extra ocular motility, confrontation visual fields and pupils were within normal limits in both eyes. Anterior segment evaluation was unremarkable OD and revealed 1+ cells and flare in the anterior chamber and vitreous OS. Ophthalmoscopy revealed a small cotton wool spot and blot hemorrhage OD. The left eye was positive for a roughly seven by four disc diameter area of elevated yellow-white granular, inflamed necrotic area in the retina with smaller satellite lesions and surrounding pigment disruption with overlying hemorrhage. The lesion followed the superior nasal vasculature with intra-retinal thickening. The disc had normal cupping with no hemes, pallor or edema. (see photos C and D). The patient was
diagnosed as having mild HIV retinopathy OD and CMV retinitis OS by clinical presentation. He was then referred to the retinal specialist on the same day who took over his care. His primary care physician was notified and the patient was admitted to the hospital for administration of IV Gancyclovir 5mg/kg along with baseline blood work to monitor for neutropenia and thrombocytopenia. The patient was instructed to follow up in the eye clinic in three days with consideration of injection of intravitreal ganciclovir if no improvement.

Follow up # 2

Three days later he was examined as an inpatient. He had been receiving IV gancyclovir 350 mg every 12 hours, blood work revealed his CD4+ count had dropped to 46 cells/ul. Best corrected visual acuity remained 20/20 OD, OS at distance and near. Anterior segment exam was unremarkable in both eyes with resolution of the anterior chamber cell OS. Vitreous findings were positive for 1+ cells and flare OS. Posterior segment was unremarkable OD and revealed improved appearance of necrotic granular appearing retina with overlying hemorrhage with less inflammation compared to three days prior OS (see photo E ). The patient was diagnosed with improved clinical appearance of CMV retinitis OS, receiving IV gancyclovir with a plan to continue current therapy with deferral of intravitreal injection given the clinical improvement and good visual acuity in both eyes. The patient was instructed to return to clinic the following day for a dilated fundus exam and a macular ocular coherence tomography (OCT) OS.

Photo E- color fundus photo of the left eye demonstrating slight regression of the CMV lesion after initiation of 350 mg IV ganciclovir every 12 hours after three days.
Follow Up # 3

On the fourth day, he was examined again as an inpatient. He reported no changes in vision and was still receiving 350mg IV gancyclovir every 12 hours. His best corrected visual acuity was 20/20 OD, OS and anterior segment exam was stable in both eyes. Posterior findings were stable compared to the exam one day prior and the macular OCT of the left eye was within normal limits with no evidence of macular involvement (photo F). Ophthalmology recommended continuation of IV gancyclovir 350mg every 12 hours and to follow up with a retinal specialist the following day.

Photo F- OCT of left macula within normal limits revealing no macular retinopathy four days after the diagnosis of CMV retinitis

Follow Up # 4, 5, 6

On days five, six and seven, he was examined by the retinal specialist as an inpatient. The patient stated that his vision was stable in both eyes at each visit. He was continually receiving 350mg IV gancyclovir every 12 hours. His best corrected visual acuity was 20/20 OD, OS and anterior and posterior segment exam continued to show no changes in either eye (see photo G). Current therapy was continued for each visit.

Photo G- CMV retinitis of the left eye showing stability after receiving 350 mg IV ganciclovir every 12 hours for five days.
Follow Up # 7

On day eight he was examined by a retinal specialist as an inpatient. All finding were stable. He was continually receiving 350mg IV Gancyclovir every 12 hours. His best corrected visual acuity was 20/20 OD, OS, and anterior and posterior segment exam continued to show no changes in either eye. He was started on an oral dose of 900 mg Valganciclovir twice per day, discharged from the hospital and educated on the importance of compliance with HAART. The patient was to follow up in the retina clinic in one week or sooner if any changes in vision.

Discussion

Cytomegalovirus (CMV) is a common opportunistic infection that occurs in an environment of immune-suppression such as with patients on immune-suppressive therapy, or patients in late stages of acquired immunodeficiency syndrome (AIDS). Immunosupersence in AIDS patients is largely based on levels of HIV virus and their level of T-helper cells, specifically the CD4+ T-lymphocyte cell which the HIV virus attacks. CMV is most opportunistic when the CD4+ count is less than 50 cells/ul and rarely seen in those with counts of more than 200 cells/ul. Normal T-lymphocyte levels range between 400 to 1700 cells/ul in healthy patients.

Primary CMV exposure usually occurs at a young age and then lies dormant in organs of immune competent individuals. It often results in end organ diseases such as cholitis, encephalitis and retinitis in up to 20% to 40% of patients with AIDS10. The most common manifestation of the virus is as CMV retinitis (CMVR), accounting for 75% to 85% of CMV disease2,10. The virus diffuses through the retina along the nerve fiber layer, and then spreads outward from retinal cell to cell, histologically resulting in full-thickness retinal necrosis3. CMVR is the leading cause of AIDS-related blindness5.

The typical presenting symptom of CMVR is painless, progressive loss of vision and is usually unilateral7. Other nonspecific complaints such as blurred or distorted vision, flashes of light, floaters, scintillations, as well as central or peripheral scotomas have been reported. Most patients have good central vision initially, with 70% to 80% having a visual acuity of 20/40 or better on presentation10.

Diagnosis of CMVR can be made based on the clinical presentation with ocular examination. Clinical findings of CMV retinitis in the anterior chamber include a mild cellular reaction and fine stellate keratic precipitates of fibrin and macrophage adherence to the corneal endothelium. Funduscopic examination can reveal inflammatory cells in the vitreous.

Retinal findings can present in two forms: hemorrhagic/fulminant type or brushfire/granular type. The hemorrhagic form is most common and begins with white retinal necrosis with overlying hemorrhages and edema in the mid peripheral retina to posterior pole of one or both eyes. The brushfire active form will show progression of the yellow-white margins with slowly advancing retinitis at the border of the atrophic retina and occurs most often in the periphery. Progression is considered advancement of an existing lesion greater than 750 microns in length and will occur without treatment5. In both forms of retinitis, the retina is non-functional. Fundus photography is recommended at least every 3 months10.
and is the best way to follow these patients to determine progression. These subtle findings differ from presenting signs of acute retinal necrosis or toxoplasmosis.

Other retinal findings include intra-retinal hemorrhages, granular appearing perivascular white exudates and a 25% to 30% chance of retinal detachment within the first 6 months and 50% to 60% chance of retinal detachment at one year\(^3\). Retinal detachments occur after the conversion of infected retina into a glial scar because as the retina becomes necrotic and thins it is susceptible to formation of multiple, poorly visualized retinal breaks\(^2\). With improved survival, retinal detachment after successful treatment and continued maintenance therapy will become increasingly frequent because the incidence of reactivation is increasing with longer life expectancy\(^2\).

CMVR lesions are often identified by location within the retina, which is divided into three zones. Zone I is defined by the area within one disc diameter of the fovea continuous with the area a half disc diameter around the optic nerve head. Zone II extends from the boundaries of zone I out to the region of the vortex ampulla. Zone III is from the border of zone II out to the ora serrata. Zone I lesions can be immediately sight threatening in a short period of time especially if temporally located. Lesions in anterior zone II and zone III are considered less sight threatening in regards to the fovea and optic nerve. However, there is chance of progression of lesions, retinal detachment and visual field constriction. CMV retinitis is considered a macular sparing disease, the fovea is rarely involved (only in about 4% of cases) and usually occurs when the retinitis is in proximity to the macula\(^8\).

Differential diagnosis includes acute retinal necrosis from herpes simplex or zoster virus, HIV retinopathy, syphilis, toxoplasmosis, bacterial or fungal endophthalmitis, large cell lymphoma and tuberculosis. These can often be narrowed by clinical appearance, the patients best corrected visual acuity and symptoms at presentation. Table A below lists the differentials with their most common clinical findings.

<table>
<thead>
<tr>
<th>Acute retinal necrosis</th>
<th>HIV retinopathy</th>
<th>Syphilis</th>
<th>Toxoplasmosis</th>
<th>Bacterial or fungal Endophthalmitis</th>
<th>CMVR</th>
<th>Large cell lymphoma</th>
<th>Tuberculosis</th>
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<tr>
<td>Retinal Hemorrhages</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>No Pain</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Immune compromised</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Very Mild Vitritis with Mild AC rxn</td>
<td>X (usually severe)</td>
<td>X (usually severe)</td>
<td>X (usually severe)</td>
<td>X (usually severe)</td>
<td>X</td>
<td>X</td>
<td>X (usually severe)</td>
</tr>
<tr>
<td>Necrotic retina</td>
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<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
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<td></td>
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Table A- Most common clinical findings of CMVR differentials at presentation
CMVR should not be confused with HIV retinopathy, which manifests as either isolated blot hemorrhages or cotton wool spots. HIV retinopathy can present similar to early stage CMVR, however, HIV retinopathy will usually be non-progressive and resolve after a few weeks. In contrast to HIV retinitis, the clinical course of CMVR can destroy the entire retina and lead to blindness within 6 months with no treatment3,4.

Laboratory testing has no role in the diagnosis of CMVR because the presence or absence of CMV antibodies neither confirms nor disproves the infection9. Atypical cases should be monitored without treatment until the clinical picture is more definitive9. For clinically apparent CMVR there are currently five virostatic treatments approved for use by the Food and Drug Administration (FDA). Foscarnet, ganciclovir, cidofovir, valciclovir and fomiviren are the current therapies approved for delivery via intravenous, oral and intravitreal injection. Successful management of CMV retinitis requires close collaboration between the ophthalmologist and the treating physician to monitor for systemic side effects.

Foscarnet, ganciclovir and cidofovir are intravenous formulations designed to systemically combat CMV. However, ganciclovir is most often used due to availability, ease of administration and side effect profile. The standard regimen for ganciclovir uses an induction dose of 5mg/kg twice daily for two to three weeks, followed by a daily maintenance dose of 5 mg/kg2. The ganciclovir intraocular implant achieves higher intravitreal concentrations than systemic forms of the drug. It is effective for five to eight months against newly diagnosed and recurrent CMV retinitis and is associated with low risk of severe intraoperative and postoperative complications2,10. The ganciclovir implant is an appropriate choice of initial therapy for CMVR, especially for patients with an immediate threat to their vision. Side effects of both drugs include neutropenia (34%) and thrombocytopenia (4%)10. When the treatment is discontinued, the retinitis recurs secondary to the virostatic nature of the drugs, so maintenance dosing is required, usually in the form of orals.

The oral form of ganciclovir is approved for maintenance therapy after intravenous induction therapy at 3000mg per day. Oral ganciclovir is less effective than the IV form, but at a higher dose of 4500 to 6000mg per day, it can be almost as effective10. The oral form has limited bioavailability so many clinicians avoid using the oral form in patients with lesions that are immediately vision threatening by proximity to the optic nerve or fovea. Oral ganciclovir should not be used as the sole form of induction therapy and should not be the sole form of maintenance therapy in patients with sight threatening disease10.

Discontinuation of maintenance therapy may be considered in patients with HAART induced elevated CD4+ counts above 100 cells/ul, prolonged intervals with no relapse during the reconstitution period, before CD4+ counts reach 100 cells/ul, and completely quiet retinitis characterized by RPE scarring only. Close observation with follow up dilated exams are indicated with discontinuation of maintenance therapy for CMVR.
The patient in this case was initially referred for an eye examination by his primary care physician secondary to his low CD4+ count. Although HIV retinopathy was mild at first exam, close follow up was critical for early detection of CMVR, as he presented with no visual symptoms and 20/20 vision in both eyes. He demonstrated the more common hemorrhagic form of CMVR with red hemorrhages overlying a white inflamed necrotic retina and edema in the mid peripheral retina beginning in zone I and extending into zone II. He also had a mild anterior chamber reaction. By his declining CD4+ count, it was apparent that his recent compliance with HAART had been poor and considering the location of the lesion it was a logical choice to admit him as an inpatient and begin immediate IV ganciclovir. The standard induction dose of 5mg/kg twice daily was administered and the patient was monitored as an inpatient. His CMVR was followed with fundus photography, the gold standard for monitoring progression, with which he demonstrated slight immediate regression and then stability of the lesion over the eight day period. The plan for any noted progression was to administer an intraocular injection of ganciclovir, to increase the concentration of drug at the site of action in this unilateral case. The patient had no other systemic manifestations of CMV, other than retinitis.

Despite drug therapy, progressive visual loss occurs over time. In a series of 287 patients with CMV retinitis, the median time to vision of 20/200 or worse in an eye with retinitis was 13.4 months and to bilateral vision of 20/200 or worse was 21.1 months. Examinations should be continued regularly even in patients with unilateral disease as they eventually tend to recur leading to vision loss. Regular examinations could help aid in early detection of new disease in the other eye.

**Conclusion**

This case demonstrates the importance of close follow up in AIDS patients with HIV retinopathy and a known history of questionable compliance with HAART. An early and accurate recognition of CMVR is imperative to avoid destruction of the posterior pole and the optic nerve which can lead to complete blindness. Patients should be educated regarding the subtle symptoms of CMVR and advised to seek care in a timely manner after onset of symptoms. Patients at high risk secondary to non-compliance with HAART therapy or low CD4+ counts, should be dilated with indirect ophthalmoscopy every three to six months. Treatment of CMVR should also be individualized on the basis of the patients living conditions, life style preferences and location of the lesion.
References:


