A Rare Case of Cytomegalovirus Retinitis with Subsequent Immune Reconstitution Uveitis

Tracy Doll O.D.
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Description
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Keywords
Cytomegalovirus, Retinitis, HIV, AIDS, Immune Reconstitution, Uveitis

Disciplines
Clinical Epidemiology | Infectious Disease | Ophthalmology | Optometry

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A Rare Case of Cytomegalovirus Retinitis with Subsequent Immune Reconstitution Uveitis

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Abstract

A routine eye exam on a young male patient finds asymptomatic retinal lesions suggestive of retinal necrosis. Confirmatory medical laboratory tests reveal a diagnosis of cytomegalovirus retinitis in the setting of an HIV infection. Subsequent treatment leads to immune reconstitution uveitis.

Key Words

Cytomegalovirus, Retinitis, HIV, AIDS, Immune Reconstitution, Uveitis

Introduction

Cytomegalovirus retinitis (CMVR) is the most common cause of blindness in patients diagnosed with AIDS. With the advent of modern HIV treatment, the CMVR rates have been dramatically reduced, but still persist. One in five patients infected with HIV are unaware they have contracted the virus. I report here on one such patient: an asymptomatic patient with CMVR in the setting of a previously undiagnosed HIV infection, with subsequent immune reconstitution uveitis. I will also discuss current treatment, prognosis and complications

Case Presentation

Subjective

A 25 year old Hispanic male, presented with a chief concern of itchy eyes for the duration of six months. He had no other visual complaints. His ocular history was unremarkable and this was his first eye examination.

His systemic history is significant only for nail fungus for which he was on an oral antifungal medication of unknown name.

Objective

Uncorrected incoming visual acuity was measured at 20/25 OD and 20/50 OS Best corrected visual acuity was 20/20 OD and 20/25- OS.
Confrontational visual fields, extra-ocular motilities and pupils were all found to be within normal limits.

External and biomicroscopy examination revealed bilateral mildly inflamed pingueculae, worse on the left eye. The anterior segments OU at that time were quiet. No inflammatory cells in the aqueous were present.

Intraocular pressures, as measured with Goldmann applanation tonometry were 8mmHg OD and OS.

Posterior examination OD was remarkable for one isolated dot blot heme in the posterior pole just off the optic nerve inferior nasal. The nerve itself was healthy with moderate cup to disc ratio.

Posterior examination OS showed a diffuse 2+ vitritis, but views of the retina were still obtainable. The posterior pole was remarkable for scattered dot-blot hemorrages. At the end of the vascular arcades extending into the peripheral retina, particularly superiorly, extensive patches of exudates, hemorrhaging and vascular sheathing adjacent to areas of white, necrotic retina were detected. The retina appeared to be attached 360 degrees. The optic nerve head was healthy and the macula was attached, though it was difficult to ascertain whether or not macular edema was present due to vitritis.

Blood pressure in office was measured at 116/72mmHg. Non-fasting blood glucose was measured at 120mg/dL. Photo-documentation of mid-peripheral lesions were taken at that time, though hazy as taken through 2+ vitreal cells. See Figures 1 and 2 below.

FIGURE 1: Posterior Pole View of Right and Left Eye
FIGURE 2: Mid-peripheral Lesion Left Eye
Assessment and Plan:
When questioned, the patient denied any pain or noticeable loss of vision out of the left eye. An immediate phone call was placed to facilitate a retinal specialist referral with a large optometric group. The patient was triaged to general ophthalmology for evaluation the next morning.

At the general ophthalmology visit, a there was a new finding of keratic precipitates on the corneal endothelium with a diffuse dendritic appearance on the left eye that had not been present the day before. The visual acuity in the left eye had dropped to 20/70 unaided. The retinal findings remained unchanged. Macular edema was confirmed OS with the use of OCT (Ocular Coherence Tomography), with central macular thickness of 302µm (Figure 3). The patient was referred to retinal specialty immediately.

Blood work and serology were ordered and the Table 1 shows the results:

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>low RBC, hemocrit and hemoglobin as well as mildly elevated levels on mononucleocytes</td>
</tr>
<tr>
<td>Chemistry</td>
<td>calcium 8.5 (nl 8.6-10.3)</td>
</tr>
</tbody>
</table>
Retinal specialty admitted the patient to a hospital for three days, where an intravenous Acyclovir regimen was started. A vitreal tap for further laboratory testing was performed and an injection of foscarnet was also performed. Aqueous and vitreal fluid were sent out for viral PCR (polymerase chain reaction) testing.

Following his hospital stay, posterior segment findings were relatively unchanged, but anterior chamber inflammation had subsided and visual acuity OS was improved to 20/30. The diagnosis of Acute Retinal Necrosis (ARN) was given, with suspect CMV-like lesions. The patient was to continue intravenous Acyclovir therapy. HIV test results had not yet returned.

The patient returned for an appointment a week later when more lab results had returned. These lab results can be seen in Table 2.

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral PCR</td>
<td>CMV DNA PCR positive</td>
</tr>
<tr>
<td>HIV Blood Test</td>
<td>Positive</td>
</tr>
<tr>
<td>CD-4/ T-Cell Count</td>
<td>68 cell/µL</td>
</tr>
</tbody>
</table>

The patient was confirmed to be infected with cytomegalovirus (CMV) in the setting of an HIV infection. The patient was to have an intravitreal injection of ganciclovir. His acyclovir intravenous treatments were stopped and oral Valcyte (vancyclovir) 900mg TID was prescribed for 3 weeks then one pill daily.

One week later the patient returned to retinal specialty with some improvement seen in the retina. Areas of whiting were less with less vitritis and improved vascular sheathing. He was set to continue with ganciclovir injections and oral Valcyte.

Ten days later, the leading edge of the retinal lesions were becoming pigmented and the vitritis was improving. Retinal specialty gave its consent for the patient to begin HAART treatment when infectious disease specialty deemed appropriate. No more injections of ganciclovir were deemed necessary. The patient was to be watched carefully in the following weeks for immune-constitution uveitis.

About one week later, the CMV retinitis was deemed completely resolved while on the HAART and Valcyte treatments.
Unfortunately, about a week later, the patient returned to the retinal specialist with concerns of eye pain. Possible mild reconstitution uveitis was detected OS, but no active CMVR. The patient’s CD4 count had risen to 154 cell/µl, with a viral load of 6400 copies/ml of plasma.

From that point on, immune reconstitution uveitis with cystoid macular edema has plagued the patient (See Figure 3).

**FIGURE 3: OCT of Cystoid Macular Edema Secondary to Immune Reconstitution Uveitis**
He was moved from retinal specialty to uveitis and inflammatory ocular disease specialty. His visual acuity has plummeted to counting fingers at 3 feet with eccentric fixation. The patient continues to be monitored at regular intervals by ophthalmology and infectious disease specialties.

Pertinent to this case, is the in-depth infectious disease medical history. The patient reported to this specialist of having a sexual history with over 30 different women within the five years prior to his HIV/AIDS diagnosis.

A flow-chart of the patient’s treatment regimen can be seen below in Table 3.

<table>
<thead>
<tr>
<th>Date</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Detection</td>
<td>Initial detection of vitritis and retinal lesions - suspect Acute Retinal Necrosis (ARN)</td>
<td>• Referral to Intermediate Site for General Ophthalmology</td>
</tr>
<tr>
<td>Next Day</td>
<td>General ophthalmology detects mild macular edema, suspects ARN</td>
<td>• Referral to Retinal Specialty</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blood work/ serology order</td>
</tr>
<tr>
<td>Day 2</td>
<td>Retinal Specialist confirms ARN with suspect CMV lesions</td>
<td>• Admitted to hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IV Acyclovir regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• A vitreal tap/ injection of foscarnet</td>
</tr>
<tr>
<td>Day 5</td>
<td>ARN diagnosed with suspect CMV lesions</td>
<td>• In-patient at Hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Aqueous and vitreal fluid were sent out for viral PCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Intravenous Acyclovir regimen</td>
</tr>
<tr>
<td>One Week</td>
<td>ARN diagnosed with suspect CMV lesions</td>
<td>• Auto- fluorescent photography</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Intravenous Acyclovir regimen</td>
</tr>
<tr>
<td>One Week + One Day</td>
<td>Cytomegalovirus retinitis (CMVR) in the setting of an HIV infection diagnosed based on lab results</td>
<td>• Intravitreal injection of ganciclovir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Acyclovir IV treatments stopped</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oral Valcyte 900mg TID for 3 weeks then one pill daily</td>
</tr>
<tr>
<td>Two Weeks</td>
<td>Cytomegalovirus Retinitis (CMVR) in the setting of an HIV infection</td>
<td>• Intravitreal injection of ganciclovir every other day for a total of 3 more</td>
</tr>
</tbody>
</table>
### Discussion

**Background**

Some demographic groups are at higher risk for contracting HIV. The fastest growing minority in the United States at this time is the Hispanic/Latino community. The patient above belongs to this demographic and so it will be discussed briefly here.

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Description</th>
<th>Treatments</th>
</tr>
</thead>
</table>
| Week 3.5   | Cytomegalovirus Retinitis (CMVR) in the setting of an HIV infection improving/ almost resolved | • OK to start HAART  
• Oral Valcyte 900mg TID |
| Week 4.5   | Cytomegalovirus Retinitis (CMVR) in the setting of an HIV infection resolved | • HAART  
• Oral Valcyte 900mg qd |
| Week 6     | Mild immune reconstitution uveitis Quiescent CMVR                            | • HAART  
• Oral Valcyte |
| 4 month, 3 weeks | Immune reconstitution Uveitis (IRU) Cystoid Macular edema (CME) Quiescent CMVR | • HAART  
• Oral Valcyte 900mg qd  
• Pred 60 mg daily (along with azithro 1200 mg once weekly per HIV MD) |
| 5 months   | Immune reconstitution Uveitis (IRU) Rapid improvement of CME                | • HAART  
• Oral Valcyte 900mg qd  
• Periocular Kenalog injections  
• Oral Pred |
| 6 months   | Resolution of CME, with little subjective VA improvement                     | • HAART  
• Oral Valcyte  
• Oral Pred tapered |
| 8 months   | CME                                                                         | • HAART  
• Oral Valcyte  
• Periocular Kenalog injection |
| 1 year     | Resolution of CME, with little subjective VA improvement                     | • HAART |
| 1.5 Year   | Resolution of CME, with little subjective VA improvement, Mild IRU           | • HAART  
• Consider Glaucoma work-up  
• Recommend discontinuation of Valcyte |
Although the Hispanic subset makes up about 16% of the current US population, they made up a disproportionate 21% of all new HIV diagnoses and accounted for 19% of all people living with HIV in the US in 2009. Since the beginning of the AIDS epidemic, an estimated 96,200 Hispanic/Latino persons have died from complications due to HIV.

The populations groups most at risk for contracting HIV, in descending order, are: Caucasian, Black and then Hispanic Men who have sex with men (MSM). Heterosexual men and women also contract HIV infection at high rates. Table 4 from the CDC shows the most at-risk populations.

Table 4: Estimated New HIV Infections in the United States, 2010, for the Most Affected Subpopulations

Source: http://www.cdc.gov/hiv/statistics/basics/ataglance.html

The cytomegalovirus (CMV) is a member of the herpes virus family. Normally a healthy immune system is able to keep CMV at bay after initial exposure. However, in patients with compromised immune systems CMV can flourish. Thus, patients who commonly contract CMV are those with the Human Immune Deficiency Virus (HIV). A retinitis associated with the CMV infection, Cytomegalovirus Retinitis (CMVR) generally occurs with CD4 T-Cell counts lower than 50 cells/µl. The mean CD4 count at the time of diagnosis is 17 cells/µL. CMVR was considered a rare condition prior to the 1980s, when the AIDS epidemic first began. The advent of modern HIV treatment (HAART) in the 1990s has dramatically reduced the incidence of the condition from around 40% in those infected with HIV to 22% (2). Still, CMVR is the main cause of blindness in HIV infected individuals with complications in the eye affecting about 80% of all patients infected with both HIV and CMV (2). The rate of CMVR infection in HIV patients with
CD4 count less than 50 cells/µL is currently reported to occur in 0.20/ person-year (PY)\(^1\). Recall that a person-year is a “statistical measure representing one person at risk of development of a disease during a period of 1 year (3).” A patient with AIDS is estimated to have a 20-40% chance of developing CMVR in a lifetime (1,2).

HAART has dramatically reduced the impact of HIV related morbidity and mortality. Still, there are 1.1 million people living with HIV in the United States. In 2011, an estimated 49,273 people were diagnosed with HIV infection (4). What is concerning is that almost 1 in 5 patients have no idea that they are infected (4).

**Presentation of CMVR**

A patient presenting with CMVR may have few to no symptoms, as was the case with the patient discussed and 15% of all diagnosed patients. If the location of the retinitis is largely peripheral, a patient may not know they are infected or present with floaters, flashes, scintillating scotomas or reduced peripheral visual field. If the retinitis is in the posterior pole, the patient may be far more symptomatic of decreased vision or scotomas. It should be noted that pain and redness of the anterior segment are rare without co-infection (1,2).

Cytomegalovirus can be unilateral or bilateral. One retrospective study of 222 cases of CMVR showed 92 patients to have bilateral disease, while 130 had unilateral disease (7). Prompt systemic treatment of unilateral cases has been associated with decreasing the rate of the condition spreading to involve the contralateral eye (7).

CMV creates lesions of full-thickness chorioretinal whitening adjacent to hemorrhages (see Figure 2). When these lesions are located anatomically from the edge of the posterior pole into the region of vortex ampula/veins (equator), this is called Zone 2. If located in the periphery, anterior to the equator (Zone 3), these lesions can be oriented circumferentially and are more granular in appearance. Retinal vasculitis, seen as white”frosting” of retinal blood vessels is common adjacent to the lesions. As the CMV progresses (often unnoticed), it leaves in its wake a path of infiltrated atrophic retinal pigmented epithelium (RPE) and chorioretinal scarring which appears neighboring the white-grey active lesions. CMVR is thought to move through the retina at about 24 µm per day if left untreated (1). Progression in clinical trials is defined as “movement of a lesion border at least 750 µm along a front that is 750 µm or more in length or the development of a new CMV lesion in the affected or fellow eye as detected by serial fundus photography (2).

Rhegmatogenous retinal detachment might be a secondary finding. Multiple breaks due to attached vitreous at the edge of necrotic tissue are to blame. A retinal detachment most often occurs within 3 to 6 months of CMVR diagnosis. With current HIV treatment (HAART) retinal detachments generally occur only in patients with more than 25% of the retina involved (1,2).
If the infection infringes into the posterior pole (Zone 1), large cotton wool spots with or without hemorrhage at the macula or papillitis can occur. Cataracts are also a common secondary finding (1,2).

Visual impairment and blindness from CMVR is usually attributable to edema of macula and nerve, retinal detachment and cataract formation.

Uveitis and vitritis specifically in response to CMV is considered rare. When a marked uveitis or vitritis is detected, it is usually secondary to a concurrent infection such as toxoplasmosis, syphilis, varicella zoster or simplex, or lymphoma (1,2). Interesting to note is that the patient above had an Immunoglobulin G response that measured high for Toxoplasma. He also had a positive Lyme titer. His vitritis is easily seen in Figure 1.

**Diagnosis of CMVR**

The diagnosis of CMVR is made based on clinical presentation confirmed with medical laboratory testing. As CMVR is rare without co-infection of HIV, (congential transmission as well as other immune-compromising disorders can leave a patient open to contracting CMVR (1)), HIV testing is standard protocol. Blood testing can be done to identify infection for HIV and samples of vitreal fluid can be obtained to identify CMV as the culprit of the retinitis.

The Enzyme Linked Immunosorbent Assay (ELISA) is a blood serum testing method, not a specific test for one kind of disease. Blood is exposed to antibodies for specific diseases in the ELISA. If a disease is present, antibodies laced with florescent markers will “stick to” the disease antigen in the serum, indicating an immune response. The main use for ELISA is as a screener for HIV (8).

The Western Blot (WB), like the ELISA is a laboratory testing method, not a specific disease test. The WB testing separates the blood sample proteins out and then exposes these proteins to specific disease antigens, leading to the detection of a disease agent (8). The WB’s main use is to confirm HIV after the ELISA screener. It is the confirmatory blood test (8).

HIV confirmation can go hand-in-hand with hematological studies. HIV targets the body’s lymphocytes known as “killer T-cells.” These cells are crucial in the immune response. The receptors on the T-Cells that bind HIV are known as CD4 receptors. Normal CD4 or T-Cell counts will range from 500 cells/ mm3 to 1,000 cells/ mm3 (You should note that in the literature, CD4 count units can be either in mm3 or in µL. One mm3 is equivalent to one µL.) HIV will lower this number. AIDS is diagnosed when the CD4 count is lower than 200 cell/ µL (9,10).

Along with measuring lowered CD4 counts, the amount of virus in a sample can indicate the level of disease. For this reason, viral loads are often reported alongside CD4 counts.
A viral load is considered “undetectable” at fewer than 40-75 copies/mL. A newly diagnosed patient may have millions of viral fragments (copies) that are detected. Usually the viral load is looked at over time to watch for trends of increase or decrease. An exact viral load number is not diagnostic of AIDS as with the CD4 count. A higher viral load would increase the chance of a lower T-Cell count.

The polymerase chain reaction test is used to identify specific viral agents, including CMV, the herpes simplex virus (HSV), and varicella zoster virus (VZV). PCR is a process where small sequences of DNA within a sample are replicated repeatedly. The DNA of the sample is compared to known DNA sequences of suspected viral entities. In this manner CMV can be confirmed.

**Treatment of CMVR**

Current treatment for CMVR is initiated as a combination of oral and intravitreal injection/ocular implanted antiviral agents. Treatment is divided into 2 phases: induction/anti-CMV and maintenance/anti-HIV therapy.

Oral Valcyte (Valganciclovir) is often the first step in induction therapy. Valcyte has excellent bioavailability and has been shown to be as effective as intravenous ganciclovir for initiation of CMVR therapy. Intravitreal or ocular implanted ganciclovir is then added in patients with Zone 1 involvement or in patients at risk for vision loss. Implanted ganciclovir can also be effective when oral treatment with ganciclovir is not efficacious or if the CMV is found to be resistant to oral ganciclovir. There are some strains of CMV that have become resistant to the classic treatment of ganciclovir and an older medication, foscarnet.

If CMVR progresses or reoccurs before the immune system can be reconstituted on systemic anti-HIV therapy (HAART), then implanted ganciclovir (Vitrisert) is recommended. This implant is also suggested in the cases where HAART is not an option for a patient due to poor compliance or response. The implant will last around 5-8 months and can be replaced every 7-8 months as needed. The implant has proven to predispose patients to the development of CMVR in the contralateral eye and raises the rates of visceral disease and mortality when this treatment is used alone. To insure systemic treatment of CMV, oral ganciclovir or valcyte is then used in conjunction.

There is a new intra-vitreal medication potentially coming down the pipelines, although it is still in animal trials at this time. Hexadecyloxypropyl-cyclic cidofovir, is a long lasting prodrug of cidofovir. This might provide an alternative for those patients who’s CMV proves resistant to classic treatments.
As was already mentioned, the advent of the modern HIV/AIDS treatment known as HAART (Highly Active Antiretroviral Therapy) has dramatically reduced the incidence of CMVR. In fact the majority of new cases of CMVR are now occurring in patients who cannot be treated with or do not respond to HAART. Once CMV is deemed no longer active through use of anti-CMV agents, the maintenance phase of treatment is initiated with the use of HAART (1).

HAART is defined as treatment with at least three active antiretroviral medications (ARV's), typically two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) or integrase inhibitor. The medications listed in Table 5 are aimed at stopping HIV replication in the body (13).

Table 5: HAART Therapy Components (14)

<table>
<thead>
<tr>
<th>HAART Medication Category</th>
<th>Common Medications Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside/nucleotide reverse transcriptase inhibitors</td>
<td>tenofovir, emtricitabine, abacavir</td>
</tr>
<tr>
<td>Non-Nucleoside/ reverse transcriptase inhibitors (NNRTs)</td>
<td>efavirenz, nevirapine, etravirine</td>
</tr>
<tr>
<td>Protease Inhibitors (PIs)</td>
<td>atazanavir, ritonavir, darunavir</td>
</tr>
<tr>
<td>Fusion and Entry Inhibitors</td>
<td>enfuvirtide and maraviroc</td>
</tr>
<tr>
<td>Integrase Inhibitors</td>
<td>raltegravir</td>
</tr>
</tbody>
</table>

Typical combinations of HAART include (14):

- Efavirenz + tenofovir + emtricitabine
- Ritonavir-boosted atazanavir + tenofovir + emtricitabine
- Ritonavir-boosted darunavir + tenofovir + emtricitabine
- Raltegravir + tenofovir + emtricitabine

HAART was originally a combination of zidovudine (AZT) in 1985, didanosine in 1991 and zalcitabine in 1992. These drugs became the foundation for new generation of HAART medications (1,12,13).

Valcyte is also used past induction into the maintenance phase of CMVR treatment. Once CMVR is deemed no longer active, oral Valcyte or anti-CMV treatment is generally continued for 3-6 months alongside systemic HAART to insure that the immune system is reconstituted. If a patient is already on HAART, anti-CMV therapy can be discontinued only once the patient has a CD4 count consistently above 100 cells/µl at two consecutive times, three months apart. The CMVR should also be inactive for more than four months. These patients are watched carefully, on average at about three month intervals to lookout for any reoccurrence. There is no CD4 count that is considered protective at this time (1).

Although CMVR rates and severity have been improved with the use of HAART, the use of HAART is not always without consequence in the eye. Immune reconstitution uveitis
(IRU) can occur when the body’s immune system recovers partially with the use of HAART.

“The AIDS Clinical Trial Group defined IRU as a ‘decrease in vision and at least two of the following signs in the absence of active CMVR: presence of >2+ inflammatory cells in vitreous by slit lamp examination, cystoid macular edema (CME) or epiretinal membrane formation in patients receiving potent antiretroviral therapy with evidence of immune reconstitution.”

Or

“NIH sponsored Studies of the Ocular Complications of AIDS is ‘the occurrence of intermediate uveitis in patients with CMVR who have evidence of immune reconstitution, as shown by a rise in CD4 T-cell counts after the initiation of HAART.”

The mechanism of how IRU occurs is not proven. The theory is that CMV antigens still exist in the eye, even when the infection is no longer active. The reconstituted immune system then attempts to fight these antigens. CMVR damage to the eye breaks down the blood-brain barrier and allows for inflammatory cells to more easily enter the eye. One study demonstrated that patients with partial versus full immune recovery tend to experience IRU more often. Other risk factors for IRU include more extensive retinal involvement in cases with more than 30% of the retina (versus only 18%) involved. The use of cidofovir for treatment is also associated with a higher incidence of IRU. Secondary complications from IRU (other than uveitis and vitritis) include optic nerve and macular edema (see figure 4 above), and epiretinal membrane/vitreomacular traction development. Retinal neovascularization can also occur.

The best treatment for IRU (and the treatment that was provided to the patient above) is systemic and ocular steroids with about a 50% success rate. Small sample case studies have also shown that steroid implants along with CMV therapy (valacyclovir/ganciclovir) can also be effective, but the subjects for this study had CD4 counts all three times the minimum of 100cell/mm3, the level needed for immune reconstitution. There is also evidence that delaying HAART therapy until the CMVR is no longer active can decrease the incidence of IRU. However the delay of HAART initiation can leave a patient open to other opportunistic infections in the body. In the patient above, the initiation of HAART therapy was deferred until the CMVR showed improvement.

Differential Diagnosis

CMVR is not the only condition that can lead to necrosis of the retina in HIV patients. Two other conditions, Acute Retinal Necrosis (ARN) and Peripheral Outer Retinal Necrosis (PORN) can also lead to devastating visual outcomes. It is important to be able to differentiate their presentation from that of CMVR.

ARN:
The atypical presentation of vitiris and uveitis in the case patient above made Acute Retinal Necrosis (ARN) the primary differential diagnosis for CMVR. Even in patients without active iritis or vitritis, ARN still rises to the top of the list for differential diagnoses.

Acute retinal necrosis, (ARN) is a rare condition, with predilection for males. It has been documented in patients aged 4 though 89 years of age, with the majority of patients between the ages of 20-50 years of age. ARN or BARN (bilateral acute retinal necrosis) has been associated with herpes simplex (HSV) and varicella zoster (HZV) viruses and in immuno-compromised patients with HIV. It is interesting to note is that AIDS patients with higher CD4 counts (>50cell/µL) can develop ARN as well as those with lower CD4 counts (2,15).

The hallmark features of ARN include significant intraocular inflammation including panuveitis, vitritis, vaso-occlusive angiitis of both the retinal and choroidal vessels, and necrotizing retinitis. This inflammation primarily affects the peripheral retina. If untreated, the condition can progress to a rhegmatogenous retinal detachment in the final stages (2,15).

The condition can progress rapidly. A patient will commonly first present with a mild reduction in vision and mild to moderate peri-orbital pain. A red eye is often present. Due to the predilection of ARN for the peripheral retina in early stages, rarely does ARN first present with dramatic central vision loss. If central vision loss is the primary concern, retinal artery occlusion or retinal detachment is usually the culprit. In the early stages ARN can be asymptomatic (2,15).

External examination can reveal variable degrees of acute inflammation. Episcleritis or scleritis can yield a red eye. A mild to moderate anterior chamber reaction with or without keratic precipitates may be present. If present, the KPs can be fine or granulomatous. If the patient has concurrent HIV and HSV infection, stromal or dendritic keratitis has been documented to occur (2,15).

Posterior segment findings are similar to CMVR. ARN begins with a diffuse vasculitis of both arteries and veins in the retina. This manifests by a distinct sheathing of the larger caliber vessels. Peripheral retinal tissue subsequently (or concurrently) begins to necrotize and form full-thickness white patchy lesions. These lesions are known as “thumb-print lesions.” Over the span of a couple of days to weeks theses lesions can go on to coalesce involving anywhere from one half of a clock hour to the entire peripheral retina (2). As the infection progresses towards the posterior pole, perivascular hemorrhages, macular edema, retinal artery occlusions and optic disc swelling can occur (2). Many times with ARN, the posterior segment signs may be more difficult to visualize, due to a concurrent vitritis. Debris from the necrotizing retina and inflammatory cells can lead to fibrovascular traction and subsequent retinal detachment late in the course of ARN syndrome (2,15).
Without treatment, ARN will “burn-out” within 6-12 weeks, leaving behind full-thickness atrophic, scarred retina and possible retinal breaks at the interface between healthy and atrophic retina. Rhegmatogenous retinal detachments can subsequently occur during the recovery stage of ARN in 50-70% of patients who go untreated. Tractional detachments can also occur commonly occur as a result of the corresponding vitritis (2,15). Current treatments are aimed at the viruses associated with ARN: HSV, VZV and HIV.

**PORN**

Peripheral Outer Necrosis (PORN) is also a good differential for CMVR. Like CMVR, PORN is also a necrotizing retinitis that commonly affects HIV/AIDS infected individuals. Like ARN, it has been associated with the herpes virus family, particularly the varicella zoster virus (HZV). PORN has also been linked to other viral etiologies including: CMV, HSV and the Epstein Barr. Prior to HAART treatment, PORN came in second to CMVR as the cause for blindness in HIV infected individuals (1).

The progression of PORN is very fast and runs its course within day to weeks. Almost 70% of cases are bilateral. PORN is linked to patients with almost no immune response (CD4< 50 cells/µL). For this reason, it is rarely associated with anterior segment inflammation or vitritis. Unlike ARN and CMVR, PORN often begins with cherry-red macular lesions in 65% of patients (1,2). The condition can first appear in the periphery and then move toward the macula as well. The initial lesions are often yellowish in color with minimal hemorrhaging. Vascular sheathing can also be seen adjacent to lesions or the veins can be completely spared (perivenular clearing). As the condition progresses, the optic nerve may become edematous and hyperemic. The retina in later stages has a “cracked-mud” appearance as retina becomes scarred. Rhegmatogenous retinal detachment occurs in 70% of PORN patients, even with treatment (1,2). The tractional detachments that are common in ARN, do not happen with PORN due to lack of vitritis. Symptoms are similar to other necrotizing retinal conditions including: photopsia, floaters, scotomas and visual acuity changes.

Current treatments are aimed at the underlying associated virus (usually HZV). Lifelong treatment is usually required to keep patients from multiple occurrences.

Table 6 (below) shows common finding that can help differentiate CMVR, ARN and PORN

<table>
<thead>
<tr>
<th>TABLE 6: Comparison of CMVR, ARN and PORN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMVR</strong></td>
</tr>
<tr>
<td>Most Common Underlying Infection</td>
</tr>
<tr>
<td>Immune Status</td>
</tr>
<tr>
<td>Appearance</td>
</tr>
</tbody>
</table>
**Location of Lesions**

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Anywhere</th>
<th>Peripheral → inward</th>
<th>Inward → Peripheral</th>
</tr>
</thead>
</table>

**Associated Inflamm**

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Rare</th>
<th>Common: uveitis or vitritis</th>
<th>Rare</th>
</tr>
</thead>
</table>

**Associated Retinal Detachment**

<table>
<thead>
<tr>
<th>Detachment</th>
<th>Rhegmatagenous</th>
<th>Rhegmatagenous or Tractional</th>
<th>Rhegmatagenous</th>
</tr>
</thead>
</table>

**Bilaterally**

<table>
<thead>
<tr>
<th>Progression</th>
<th>Either</th>
<th>Unilateral</th>
<th>Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 µm per day</td>
<td>6-12 weeks</td>
<td>Fast: Days to Weeks</td>
<td></td>
</tr>
</tbody>
</table>

Other infectious conditions that can be associated with vitritis include syphilis, toxoplasmosis and tuberculosis. These conditions may also have associated retinitis with lesions. In HIV infected individuals it is not uncommon for other infections to be comorbid with CMV. For this reason, medical laboratory tests are run to rule out other infections. Table 7 below lists medical laboratory tests ordered alongside HIV/CMVR testing. It is interesting to note that in the case presentation above, the patient did test show higher levels of IgG, indicating exposure to toxoplasmosis.

**TABLE 7- Infectious Disease and Medical Laboratory Tests**

<table>
<thead>
<tr>
<th>Infectious Disease</th>
<th>Medical Laboratory Test</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasma</td>
<td>IgG, IgM</td>
<td>IgG indicates infection for likely &gt;1 year, IgM &lt;1 year</td>
</tr>
<tr>
<td>Syphilis</td>
<td>VDRL (Venereal Disease Research Laboratory), RPR (Rapid Plasma Reagin), FTA-ABS (Fluorescent Treponemal Antibody Absorption Test)</td>
<td>VDRL and RPR are screening tests, while FTA-ABS is confirmatory</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>PPD (Purified Protein derivative skin test)</td>
<td>Indicates exposure. &gt;5mm is considered a (+) test on an HIV patient</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>ACE (Angiotensin Converting Enzyme)</td>
<td>ACE is 75% sensitive for sarcoid and; it is 95% specific if combined with a gallium scan and chest x-ray</td>
</tr>
<tr>
<td>Lyme Disease</td>
<td>Lyme Titer</td>
<td></td>
</tr>
</tbody>
</table>

There are other differential diagnoses that should be considered for CMVR, other than infectious causes. Leukemia retinal lesions can have a very similar appearance to the lesions seen in CMVR. In this case the lesions are white-centered hemorrhages and cotton wool spots. Other changes you might see with leukemia infiltration of the retina include vitreo-retinal neovascularization, vein occlusion, vitreous and choroidal
hemorrhage. Optic neuropathy can also be seen. Biopsy of the ocular tissues involved is considered diagnostic (17).

Vascular occlusions should also be considered as the appearance of large hemorrhages with adjacent retinal exudates can look very similar to the lesion seen in CMVR (Figure 4). The most common cause of vascular occlusion is systemic hypertension and the other systemic vascular disease. In office measurement of blood pressure and sugar are useful to screen for hypertension and diabetes. Medical laboratory blood testing including CBC with differential, cholesterol panels, and HbA1c can all help to elicit the underlying cause of a retinal vein occlusion (8).

**FIGURE 4: Branch Retinal Vein Occlusion**

Source: Pacific University College of Optometry

**Other Ocular Signs of HIV**

There are other signs of HIV that can manifest in the eye other than CMV and the previously mentioned secondary opportunistic infections. One of the most common signs of HIV is microvascular changes in the retina known as “HIV retinopathy.” Multiple cotton wool spots and retinal hemorrhages can be seen throughout the posterior pole.

Another potential ocular sign of HIV infection is the presence of skin, eyelid or conjunctival lesions called Kaposi Sarcoma (KS). KS has been linked to infection with a virus in the herpes family (HHV-8). This virus is thought to encourage the growth of abnormal cells (Figure 5) (18). KS is generally found in AIDS patients with associated lower CD4 counts.

**Figure 5: Kaposi’s Sarcoma on Eyelid**
Other opportunistic infections can target the anterior segment including herpes simplex and zoster. Molluscum contagiosum lesions can also occur due to a poxvirus (Figure 6).

**Figure 6: Molluscum contagiosum lesion**

Cytologmegalovirus retinitis (CMVR) is a condition affecting primarily HIV/ AIDS infected individuals. CMVR is the leading cause of blindness within this population. With the advent of modern HIV treatment, CMVR rates have been dramatically reduced. Still AIDS and HIV are not gone, and almost 1 in 5 patients are not aware they are infected with this devastating disease. The public health implications of detecting CMVR, as well as the impact on the individual patient are quite serious. In this case, medical laboratory testing was the key to the final diagnosis.

The patient above is also a hallmark example of the importance of routine dilation of all new patients. Not all patients who appear healthy are in-fact healthy.


