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Evaluation and Management of Uveitis in a Patient With AIDS With Low CD4 Count and Prior CMV Retinitis

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Abstract

Purpose: To report an unusual case of uveitis in a patient with AIDS and a low CD4 count. **Methods:** A single case was evaluated. **Results:** A 28-year-old man with AIDS, central nervous system lymphoma, and cytomegalovirus (CMV) viremia developed subacute vitritis in the left eye. He reported 1 month of blurry vision 2 years after initiating antiretroviral therapy. On presentation, his CD4 count was 40 cells/mm^3 and HIV viral load was undetectable. He received empiric intravenous antiviral therapy and declined intravitreal injections. Due to worsening clinical course, diagnostic and therapeutic vitrectomy was performed, and intraoperative examination was consistent with prior CMV infection. Aqueous polymerase chain reaction (PCR) was positive for CMV. Infectious workup was otherwise unremarkable. Vitreous cytology and flow cytometry were negative for vitreoretinal lymphoma. **Conclusions:** Immune recovery uveitis from CMV retinitis should be included in the differential for subacute vitritis in a patient with AIDS and low (<50) CD4 count on antiretroviral therapy.

Keywords

CMV retinitis, vitritis, immune recovery uveitis, HIV/AIDS, antiretroviral therapy, vitreoretinal lymphoma

Introduction

Cytomegalovirus (CMV) retinitis is a common late-stage AIDS complication in patients with a CD4 cell count less than 50 cells/mm^3. It presents with perivascular yellow-white retinal lesions frequently associated with retinal hemorrhage.[1] While patients with AIDS and CMV retinitis typically have minimal or no clinical vitritis due to the underlying immunosuppressed state,[2] transient vitritis reflecting new or increased noninfectious intraocular inflammation is the primary manifestation of immune recovery uveitis . Immune recovery uveitis was first described in 1998 in patients with AIDS and CMV retinitis who experienced antiretroviral therapy-mediated increases in CD4 cell count.[2,3] It is the most common form of immune reconstitution inflammatory syndrome in patients with HIV and CMV retinitis.[4]

Although there are no definite criteria for immune recovery uveitis currently, it is recognized by new or increased noninfectious intraocular inflammation in patients with AIDS and CMV retinitis who demonstrate an immune response to antiretroviral therapy, including a decrease in plasma levels of HIV RNA and an increase in CD4 cell count.[4] Immune recovery uveitis is associated with an increase in CD4 cell count to at least 100 cells/mm^3 and inactive CMV retinitis, although Immune recovery uveitis cases with CD4 count less than 100 cells/mm^3 and cases with active CMV retinitis have been reported.[5–7] The interval between the start of antiretroviral therapy and onset of immune recovery uveitis has been previously cited to range from 4 months to 2.5 years.[8] The differential for acute to subacute vitritis is large and includes uveitic entities, including acute retinal necrosis and other forms of retinitis, autoimmune etiologies and intraocular vitreoretinal lymphoma. We report an unusual case of subacute vitritis in a patient with HIV/AIDS with a CD4 cell count of 40, with immune recovery uveitis from CMV retinitis being highest on the differential.

Case Report

A 28-year-old man presented with progressive left eye blurry vision and pain for the past month. He was initially admitted to the hospital for acute onset diarrhea and workup of multiple

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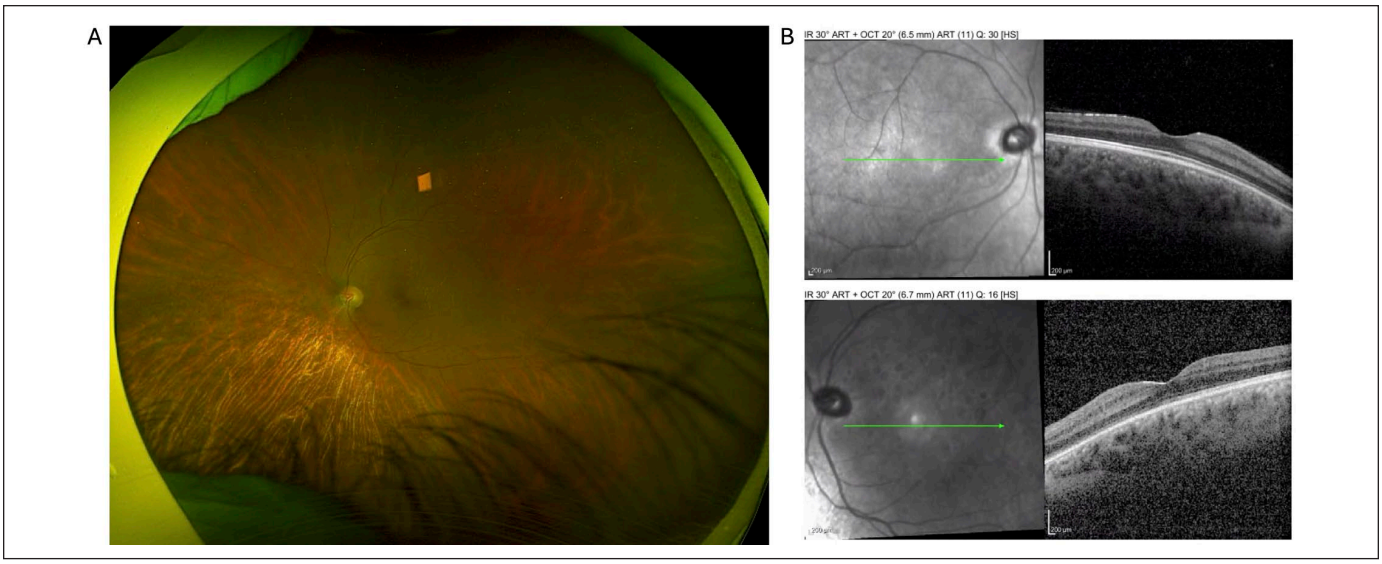

Figure 1. (A) Color fundus photo of the left eye 2 weeks after vitrectomy with no evidence of new vitritis or retinal lesions. (B) OCT shows the macula of the right (top) and left (bottom) eye.

new lytic lesions within the thoracic and lumbar spine on computed tomography imaging, along with new liver cirrhosis. Past medical history was significant for HIV/AIDS (on antiretroviral therapy with Truvada/Dolutegravir since 2022) complicated by cryptococcal meningitis and disseminated mycobacterium avium-intracellular complex, central nervous system (CNS) diffuse large B-cell lymphoma status post suboccipital craniotomy and 3 cycles of high-dose methotrexate in remission, and gastric mucosa-associated lymphoid tissue lymphoma. There was no prior ocular history. Pertinent systemic medications included anticoagulation, antiretroviral therapy, antifungal, rifampin, isoniazid, pyrazinamide, and ethambutol therapy, although adherence was limited by poor oral intake at home. On this admission, the patient had a CD4 cell count of 40 cells/mm^3 and the viral load was non-detectable.

On bedside examination, visual acuity was 20/25 in the right eye and 20/70 in the left eye. Anterior segment examination was unremarkable by portable slit lamp. Dilated examination was normal in the right eye and notable for grade 2 vitritis with vitreous condensations and loculations with a cobweb appearance overlying the posterior pole. There was no optic nerve edema, retinal vasculitis, or hemorrhage seen. Aqueous sample from the anterior chamber was obtained and sent for herpes simplex virus (HSV), CMV, varicella zoster virus (VZV), and toxoplasmosis polymerase chain reaction (PCR), as well as bacterial and fungal cultures. The patient declined further bedside eye procedures, including intravitreal antivirals, but was empirically started on systemic intravenous acyclovir 10 mg/kg every 8 hours and then transitioned to valacyclovir 1 g 3 times per day for possible herpesvirus retinitis. There was lower suspicion for CMV retinitis at this point, given the presence of significant vitritis. One week later, the vision in the left eye had worsened to hand-motion with increased vitreous condensations and grade 4 vitritis. Due to clinical progression on antiviral therapy and suspicion of vitreoretinal lymphoma, the patient underwent diagnostic and therapeutic pars-plana vitrectomy with vitreous biopsy (Supplemental Video 1) that was sent for flow cytometry, cytology, and B-cell gene rearrangement/clonality analysis PCR to rule out lymphoma. Intraoperatively, there was noted to be a nasal ridge of well-demarcated pre-retinal whitening and an inferonasal area of chorioretinal atrophy, without evidence of retinal vasculitis or hemorrhage, that appeared consistent with prior CMV infection.

The patient was found to have CMV viremia along with positive aqueous CMV PCR. Other infectious workup, including QuantiFERON-TB Gold, bronchoalveolar lavage acid-fast bacillus AFB, rapid plasmin reagin (RPR), and aqueous PCR for VZV, HSV, and toxoplasmosis, were negative. Vitreous sample was negative for B-cell population on cytology and flow cytometry. Clonal B-cell gene rearrangement was noted on PCR analysis, although this has also been reported to occur in some reactive conditions and was a nonspecific finding.[9] Myeloid differentiation primary response gene 88 (*MYD88*) mutation was negative. Recent MRI brain did not show evidence of recurrent CNS lymphoma. Valacyclovir was stopped after 7 days due to negative aqueous HSV and VZV PCR. Intraoperative intravitreal ganciclovir was deferred, despite positive aqueous PCR for CMV, due to the absence of active retinitis noted during vitrectomy. Without evidence of active end-organ infiltration by CMV, infectious disease specialists recommended holding off on starting systemic ganciclovir due to the significant risks of myelosuppression in a patient with severe leukopenia (white blood cell count 1.4 k/μL).

Two weeks after vitrectomy, vision was 20/70 in the operated eye. There was no evidence of vitritis or new retinal lesions (Figure 1, A). On OCT of the macula, he was noted to have mild sub-foveal ellipsoid zone attenuation (Figure 1, B). On follow-up 6 weeks later, vision and examination remained stable. Unfortunately, the patient was subsequently lost to follow-up.

Conclusions

In summary, this was a patient with HIV/AIDS, CNS lymphoma, and CMV viremia who developed subacute vitritis in the left eye, with immune recovery uveitis secondary to CMV retinitis being highest on the differential despite a low CD4 cell count.

There was a strong suspicion of vitreoretinal lymphoma given the appearance of the vitreous loculations and history of CNS lymphoma. Still, vitreous cytology and flow cytometry were negative for findings consistent with VRL. While these tests are the first diagnostic steps, they have been previously shown to have relatively low sensitivity and specificity.[10] Testing ocular fluids for *MYD88*—a mutation that is present in about 75% of cases of vitreoretinal lymphoma—is now an important diagnostic modality and was additionally negative in this case.[11] While up to 98% of patients with primary CNS lymphoma have contrast-enhancing lesions on initial imaging, MRI does not commonly detect intraocular vitreoretinal lymphoma.[12,13] Given the patient's history of CNS lymphoma and vitritis in the setting of significant immunosuppression, the negative workup makes the suspicion for intraocular vitreoretinal lymphoma lower but does not definitively rule it out as an etiology.

Serum and aqueous PCR were positive for CMV. Serum syphilis as well as aqueous PCR for VZV, HSV, and toxoplasmosis were negative. Workup for active tuberculosis, including serum QuantiFERON gold and bronchoalveolar lavage acid-fast bacillus and mycobacterium tuberculosis complex PCR tests, was negative. There was low suspicion for endogenous endophthalmitis given the eye was otherwise white and quiet, as well as multiple negative blood cultures.

Positive serum and aqueous CMV PCR, as well as intraoperative retinal findings of well-demarcated preretinal whitening and chorioretinal atrophy following clearing of vitreous debris, all supported the diagnosis of ocular CMV with inactive retinitis. Given that vitritis in an immunosuppressed patient on antiretroviral therapy was the defining presentation, along with no clinical features to suggest active CMV retinitis and no recurrence of vitritis 6 weeks after vitrectomy, immune recovery uveitis was highest on the differential. The patient was initiated on antiretroviral therapy in 2022, but he endorsed inconsistent adherence at home due to poor oral intake and had a CD4 count of 40 cells/mm^3 on presentation. Three months prior, he was hospitalized for 4 weeks and was on consistent antiretroviral therapy during that period. This may have been sufficient to allow him to mount an immune response, as reflected by his undetectable viral load. In addition, the patient developed worsening vitritis after being initiated on consistent inpatient antiretroviral therapy during this admission.

The accepted definition of immune recovery requires an antiretroviral therapy-mediated elevation of CD4 cell count over 100 cells/mm^3 for at least 2 months, and the majority of reported cases of immune recovery uveitis have been in patients with a CD4 cell count of at least 100 cells/mm^3.[6] There was 1 prior case report of a patient with bilateral vitritis attributed to immune recovery uveitis and a CD4 cell count of 20 cells/mm^3 or less,[5] although that patient had active CMV retinitis with frosted branch angiitis and our patient appeared to have inactive CMV retinitis. While the total CD4 cell count is generally used to evaluate the function of the immune system, there is high variability in the reconstitution capacity of the immune system in AIDS patients, and low reliability of the current assays in predicting this capacity.[5] Rather than the total number of CD4 cells, it may be the presence of surviving CD4 cells against CMV that is more important in developing a competent immune response.[14] Consequently, it has been proposed that a marked decrease in HIV mRNA level rather than an increase in absolute CD4 cell count should be regarded as the major criterion for diagnosing immune reconstitution inflammatory syndrome after initiation of antiretroviral therapy.[14,15] In our patient, an undetectable viral load was likely more reflective of immune system function.

Immune recovery uveitis has also been recently reported in patients with recovery from immunosuppression due to other etiologies—including lymphoma, leukemia, and after renal and bone marrow transplant—that require immunosuppressive treatment.[16] Alternative etiologies of immune reconstitution should be considered for this patient with a prior history of CNS lymphoma treated with high-dose methotrexate. However, the last chemotherapy treatment was 2 years prior, which thereby makes immunosuppression reduction unlikely to be the cause. Additionally, our patient had no history of taking medications known to produce uveitis, such as rifabutin or cidofovir.[17]

Roadblocks to a definite diagnosis in this case included limitations in diagnostic testing, along with patient reluctance for additional diagnostic procedures and therapies. While the treatment for CMV retinitis and CNS lymphoma differ drastically, both have significant treatment and prognosis implications and should remain on the differential in patients who present with subacute vitritis and immunosuppression. In addition, this case serves as a reminder that immune recovery uveitis secondary to CMV retinitis should not be excluded from the differential for subacute vitritis in a patient with AIDS and low CD4 cell count on antiretroviral therapy.

Ethical Approval

Due to the nature of the study, IRB approval or informed consent was not needed.

Statement of Informed Consent

Due to the nature of the study, informed consent was not needed.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material is available online with this article.

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