Flinders UNIVERSITY

Uveitis in Human Immunodeficiency Virus-Infected Individuals

Short title: Uveitis in HIV-Infected Individuals

Jane M. Wells, BMBS, BSc (Optom) and Justine R. Smith, FRANZCO, PhD

Eye & Vision Health, Flinders University, Adelaide, South Australia, Australia

Corresponding Author: Justine R. Smith, FRANZCO, PhD (Address: Flinders University School of Medicine, Flinders Medical Centre Room 4E-431, Flinders Drive, Bedford Park, SA 5042, Australia; Telephone: 61-8-8204-4300; Email: justine.smith@flinders.edu.au).

Support: Australian Research Council (FT130101648)

Abstract

Both infectious and non-infectious forms of uveitis may occur in persons who test positively for the human immunodeficiency virus (HIV). As the use of highly active anti-retroviral therapy (HAART) has become standard of care in many countries, the spectrum of uveitis has changed in this group of people. Opportunistic infectious diseases, including cytomegalovirus (CMV) retinitis, continue to occur in HIV-positive patients who suffer from AIDS. Amongst immune competent persons, syphilis is a common cause of infectious uveitis. Several uveitic syndromes that respond to HAART have been specifically associated with HIV. Immune recovery uveitis is a common non-infectious uveitis in HAART-treated HIV-positive persons with a history of CMV retinitis. Other non-infectious forms of uveitis that occur in HIV-negative individuals may also affect HIV-positive persons, although the latter group may have a higher risk of entities such as HLA B27-associated uveitis, drug-induced uveitis and vitreoretinal lymphoma. This review presents an overview of the causes of uveitis in HIV-positive people. A comprehensive ocular and systemic history and examination, with directed testing, is recommended for all HIV-positive persons presenting with uveitis, due to the broad spectrum of diseases that may be associated with uveitis in these individuals.

Introduction

Since the first description in 1982 of ocular involvement in individuals testing positive for human immunodeficiency virus (HIV),[1] a large volume of work has described the spectrum of uveitis that may occur in the setting of HIV infection. Uveitic diseases in persons infected with HIV include both non-infectious and infectious forms. Arguably the most important milestone in the management of HIV-associated disease, including acquired immunodeficiency syndrome (AIDS), has been the introduction of highly active anti-retroviral therapy (HAART) in the mid-1990s.[2] This treatment approach has dramatically changed the course of HIV infection across the globe, with reduced prevalence of and morbidity from opportunistic infections, including most notably from the ophthalmic perspective, cytomegalovirus (CMV) retinitis.

Determining the cause of uveitis in patients infected with HIV may be challenging, due to altered disease processes – and consequently atypical clinical manifestations – in the face of current or previous immune compromise and/or related to co-infection with HIV. In this review we describe the causes of uveitis in HIV-positive persons, considering both infectious and non-infectious entities. It is beyond the scope of the review to discuss management, but readers are referred to the multiple reviews of specific entities, including those appearing in this series of publications.

Non-Infectious Uveitis

The non-infectious forms of uveitis include diseases that are seen almost exclusively in individuals who are HIV-positive, including immune recovery uveitis, cidofivir-associated uveitis and diffuse lymphocytosis syndrome. However, conditions that are seen in HIV-negative persons may also occur in an HIV-infected person, including HLA-

B27-associated uveitis, sarcoidosis-related uveitis, and vitreoretinal lymphoma. While infectious uveitis accounts for the vast majority of cases in persons with relatively low CD4+ T cell levels, for the group with peripheral CD4+ T cell count above 200 cells/μl, approximately 35% of uveitis is reported to be undifferentiated or idiopathic.[3]

Immune Recovery Uveitis

Immune recovery uveitis refers to uveitis that typically occurs in an individual with AIDS and a history of CMV retinitis, whose immune function has improved after the initiation of HAART.[4] The disease represents an immune response directed against residual CMV antigens within the eye. Prevalence of immune recovery uveitis has been reported at 9.6% of patients with AIDS and CMV retinitis, in a large study involving 539 eyes of 374 patients.[5] In immune recovered HIV-positive individuals with CD4+ T cell counts over 200 cells/μl, approximately 15% of all uveitis may caused by this syndrome.[3]

Immune recovery uveitis is manifest as anterior and/or intermediate uveitis, and the inflammation may be unilateral or bilateral, depending on the laterality of previous CMV retinitis. A CD4+ T lymphocyte count above 100 cells/μl predicts the risk of uveitis.[5] Affected patients may be visually compromised in the long term following the development of cystoid macular edema and/or formation of epiretinal membrane at the macula. The severity of immune recovery uveitis may be reduced if commencement of HAART is delayed until specific treatment against CMV has been administered.[6]

HLA-B27–Associated Uveitis

HIA-B27-associated uveitis is the most common specific form of non-infectious uveitis in the general population. Affected persons may suffer one of several forms of sero-negative spondyloarthropathy as co-morbidity, or uveitis alone. The typical HLA-B27 syndrome of recurrent, unilateral alternating, acute, anterior uveitis is reported in patients infected with HIV.[3] Infection with HIV appears to facilitate the development of HLA-B27-related diseases, including both the sero-negative spondyloarthropathies and uveitis.[7,8]

Sarcoidosis-Related Uveitis

The occurrence of sarcoidosis is impacted by the presence HIV infection, due to the prominent role of CD4+ T cells in the non-caseating granulomas that are the hallmark of this multisystem disorder. Thus, sarcoidosis is exceedingly rare when the CD4+ T cell count is under 200 cells/µl, but it is an established diagnosis in patients who have either not experienced a significant decline in CD4+ T cell numbers or are immune reconstituted after the institution of HAART.[9] Indeed, sarcoidosis is reported as a cause of non-infectious uveitis in patients with relative immune competence.[3] Interestingly, the onset of typical bilateral, granulomatous panuveitis, along with skin lesions that were histopathologically diagnosed as sarcoidosis, has been temporally linked to the commencement of HAART.[10]

Other Non-Infectious Uveitic Diseases

Drug-induced intraocular inflammation is an important subset of HIV infection-associated uveitis. Rifabutin is used in the treatment of atypical mycobacterial infections, particularly *Mycobacterium avium* complex. Treatment with rifabutin may

trigger anterior uveitis, often with a hypopyon, in immune competent and compromised persons; in patients with AIDS, the risk of uveitis is strongly dependent on body weight.[11] Cidofovir was commonly used to treat CMV retinitis prior to the era of locally delivered ganciclovir. Such treatment was frequently complicated by uveitis, which usually was anterior and could be associated with hypotony.[12]

Vitreoretinal lymphoma is the most common uveitis masquerade syndrome in adults presenting with uveitis, causing intermediate uveitis and/or posterior uveitis with retinal infiltrates and retinal vasculitis. As is the case for the systemic lymphomas, the incidence of primary central nervous system lymphoma, including the vitreoretinal subset, is increased in those who are HIV-positive in comparison to those who are HIV-negative.[13] This phenomenon applies to persons who have not yet developed AIDS, as well as AIDS sufferers.[14] Reasons include up-regulation of cytokines that activate B cells, opportunistic infections with oncogenic viruses, and the state of immune compromise.[15]

Uveitis has been described in HIV-positive patients who suffer from the diffuse infiltrative lymphocytosis syndrome. This syndrome is characterized by proliferation of CD8+ T cells, with infiltration of systemic organs. Panuveitis with retinal vasculitis plus/minus retinal infiltrates in affected patients has been described in two reports.[3,16]

Infectious uveitis

The forms of infectious uveitis that occur in an HIV-positive individual may vary with immune status. For persons who have suffered immune depletion, CMV retinitis is by far the most common intraocular infection. In immune competent or recovered persons, ocular syphilis accounts for about half of cases of infectious uveitis. Herpes virus

infections, ocular tuberculosis and uveitis related to HIV occur irrespective of immune status.

Cytomegalovirus Retinitis

As documented in detail by the many reports of the Studies of Ocular Complications of AIDS (SOCA) Research Group, CMV necrotizing retinitis is the most common ocular opportunistic infection in immune compromised HIV-positive patients, clinically manifesting when the CD4+ T cell count falls below 100 cells/μl.[17,18] The introduction of HAART has been associated with an 80 - 90% reduction in the life-time incidence of CMV retinitis from approximately 30% of patients with AIDS.[19] Unfortunately HAART has not eliminated CMV infection in immune compromised patients, and albeit infrequently, HAART-treated patients with pre-existing CMV retinitis may experience progression despite achieving immune recovery. These patients remain at risk of significant visual acuity loss.[20] However, the majority of patients who develop CMV retinitis today, are those who have limited access to or are non-compliant with HAART.

Syphilitic uveitis

Hand-in-hand with the increasing incidence of syphilis in many parts of the world, is the increasingly frequent co-infection with HIV.[21] This phenomenon extends to the eye. As one example, in a study published in 2014 that included 61 HIV-infected patients with peripheral CD4+T cells counts above 200 cell/μl, syphilitic uveitis accounted for a little over 15% of all uveitis and 50% of infectious uveitis.[3] The prospective population-based British Ocular Syphilis Study (BOSS)[22] is one of several to report that syphilitic uveitis in HIV-positive patients is more likely to involve the retina, compared with disease in HIV-negative patients. Specific forms of uveitis that suggest the diagnosis of syphilis in an

HIV-positive person include necrotizing ARN-like retinitis, posterior placoid chorioretinitis and punctate inner retinitis.[23,24] However, the possibility of syphilis should be considered in all cases of uveitis presenting in HIV-positive individuals. Serological testing should include both treponemal and non-treponemal investigations, recognizing that co-infection with HIV disease may cause false positive and false negative results.

Toxoplasmic retinochoroiditis

Retinal infection with the parasite, *Toxoplasma gondii*, is the most common form of posterior uveitis worldwide. The disease may occur in HIV-positive individuals who are immune competent or immune compromised; in immune competent persons, a "typical presentation" may be expected, but in immune compromised patients an "atypical presentation" is the rule. In particular, in HIV-positive persons with peripheral CD4+ T cells counts under 100 cell/µl,[25] toxoplasmic retinochoroiditis is aggressive, with active lesions that are large and may be multiple and/or bilateral. Disease may be acquired or spread from a non-ocular site, and in this situation, the typical adjacent retinochoroidal scar is not present. In some cases, the infection may progress as an endophthalmitis and/or orbital cellulitis.

Tuberculous uveitis

Several reports of tuberculous uveitis in HIV-positive patients have been published. One of the largest patient groups was treated at Sankara Nethralaya Medical Research Foundation;[26] in 766 HIV-positive persons with ophthalmic symptoms and/or AIDS presenting consecutively, 15 cases of ocular tuberculosis were identified. All patients had pulmonary tuberculosis. Uveitis presentations included choroidal granuloma,

subretinal abscess and panophthalmitis. There was no correlation with CD4+ T cell counts, highlighting the point that ocular tuberculosis may occur over a wide range of peripheral CD4+ T cell counts, including those consistent with immune competence.

Herpes virus ocular infections

Varicella zoster virus and herpes simplex virus infections may cause anterior or posterior uveitis. Herpetic anterior uveitis is unilateral, may become recurrent or chronic, and generally includes the specific features of iris atrophy and ocular hypertension. Varicella zoster infection occurs in the context of herpes zoster ophthalmicus, and herpes simplex uveitis is often associated with keratitis. By the classic study conducted at the San Francisco General Hospital in the 1990s,[27] herpes zoster ophthalmicus has an elevated risk ratio and rate difference for HIV-positive persons, compared with HIV-negative persons. Recent data from Groote Schuur Hospital[28] indicate that HIV-positive persons are approximately twice as likely to develop uveitis as a complication of herpes zoster ophthalmicus than HIV-negative persons. These differences between HIV-positive and HIV-negative individuals do not appear to apply to herpes simplex virus infections. Based on these observations, it is standard to test apparently healthy young adults presenting with herpes zoster ophthalmicus for HIV infection.

Herpetic posterior uveitis may present as acute retinal necrosis or non-necrotizing retinitis, as also may affect HIV-negative patients who have no other medical diseases, or as progressive outer retinal necrosis. Progressive outer retinal necrosis is an extremely rapidly progressive retinitis that occurs almost exclusively in patients with AIDS and when the peripheral CD4+ T cell count is less than 50 cells/μl. It is more commonly

bilateral. The largest published series of progressive outer retinal necrosis, including 67 eyes of 39 patients living in South Africa, shows that despite aggressive treatment, approximately 50% of eyes have a final visual acuity below 20/200 and a similar percentage will suffer retinal detachment.[29]

Human Immunodeficiency Virus-Induced Uveitis

Inflammation within the eye has been specifically associated with HIV infection. A form of posterior uveitis, characterized by small multifocal retinal infiltrates and responsive to anti-retroviral therapy, was first described in the 1990s.[30] In some affected patients, the clinical picture includes anterior and intermediate eye involvement, and is more consistent with panuveitis. Recent research[31] has applied the latest in PCR technology for intraocular fluid analysis, to HIV-positive persons with anterior or anterior/intermediate uveitis that would otherwise be considered undifferentiated. In a group of 6 patients, the presence of HIV RNA in the anterior chamber, at levels far exceeding those found in the plasma, and without evidence of infectious agents other than the HIV, strongly suggested the possibility of uveitis directly related to HIV infection. The uveitis was unresponsive to corticosteroid treatment, but responded promptly to institution of HAART.

Other Infectious Uveitic Diseases

In one of their studies of the incidence and clinical outcomes of ocular opportunistic infections in patients with AIDS,[17] the SOCA Research Group identified the following pathogens as causes of posterior uveitis in the form of choroiditis: *Pneumocystis carinii*, *Cryptococcus neoformans* and *Mycobacterium avium* complex. Overall, such infections were rare, accounting for 10 of the 571 cases of infectious uveitis in the cohort of 2,362

patients. HIV-positive patients also may present with forms of infectious uveitis seen in HIV-negative patients, including entities such as bartonellosis, toxocariasis, histoplasmosis and diffuse unilateral subacute neuroretinitis.

Conclusion

In this era of HAART, HIV-positive persons remain at risk of serious intraocular infections. Although the prevalence of CMV retinitis has significantly decreased, the incidence of syphilis is increasing, and those infections are not restricted to HIV-positive individuals with low peripheral CD4+ T cell levels. Non-infectious causes of uveitis must also be considered in persons infected with HIV. After commencement of HAART, immune recovery uveitis is a common problem for persons with previous CMV retinitis, and there is the potential for immune-mediated disease to be unmasked. We advocate a comprehensive ocular and systemic history and examination, with directed testing, for all HIV-positive persons presenting with uveitis, owing to the broad spectrum of uveitis diseases and the atypical presentations of some forms of uveitis in these individuals.

References

1. Holland GN, Gottlieb MS, Yee RD, et al. Ocular disorders associated with a new severe acquired cellular immunodeficiency syndrome. Am J Ophthalmol 1982;93:393-402.
2. Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. New Eng J Med 1998;338:853-860.
3. Rose-Nussbaumer J, Goldstein DA, Thorne JE, et al. Uveitis in human immunodeficiency virus-infected persons with CD4+ T-lymphocyte count over 200 cells/mL. Clin Exp Ophthalmol 2014;42:118-125.
4. Holland GN. Immune recovery uveitis. Ocul Immunol Inflamm 1999;7:215-221.
5. Kempen JH, Min YI, Freeman WR, et al. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. Ophthalmology 2006;113:684-694.
6. Ortega-Larrocea G, Espinosa E, Reyes-Teran G. Lower incidence and severity of cytomegalovirus-associated immune recovery uveitis in HIV-infected patients with delayed highly active antiretroviral therapy. Aids 2005;19:735-738.
7. Njobvu P, McGill P. Human immunodeficiency virus related reactive arthritis in Zambia. J Rheumatol 2005;32:1299-1304.
8. Njobvu P, McGill P, Kerr H, et al. Spondyloarthropathy and human immunodeficiency virus infection in Zambia. J Rheumatol 1998;25:1553-1559.
9. Morris DG, Jasmer RM, Huang L, et al Sarcoidosis following HIV infection: evidence for CD4+ lymphocyte dependence. Chest. 2003;124:929-935.

10. Pascual JC, Belinchon I, Silvestre JF, et al. Sarcoidosis after highly active antiretroviral therapy in a patient with AIDS. Clin Exp Dermatol 2004;29:156-158.
11. Shafran SD, Singer J, Zarowny DP, et al. Determinants of rifabutin-associated uveitis in patients treated with rifabutin, clarithromycin, and ethambutol for Mycobacterium avium complex bacteremia: a multivariate analysis. Canadian HIV Trials Network Protocol 010 Study Group. J Infect Dis 1998;177:252-255.
12. Davis JL, Taskintuna I, Freeman WR, et al. Iritis and hypotony after treatment with intravenous cidofovir for cytomegalovirus retinitis. Arch Ophthalmol 1997;115:733-737.
13. Rosenblum ML, Levy RM, Bredesen DE, et al. Primary central nervous system lymphomas in patients with AIDS. Ann Neurol 1988;23 Suppl:S13-16.
14. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer 2008;123:187-194.
15. Knowles DM. Etiology and pathogenesis of AIDS-related non-Hodgkin's lymphoma. Hematol Oncol Clin North Am 2003;17:785-820.
16. De Silva DJ, Obi AA, Mitchell SM. Bilateral panuveitis in HIV-1-infected patients with CD8 lymphocytosis. Ocul Immunol Inflamm 2005;13:311-316.
17. Gangaputra S, Drye L, Vaidya V, et al. Non-cytomegalovirus ocular opportunistic infections in patients with acquired immunodeficiency syndrome. Am J Ophthalmol 2013;155:206-212 e205.
18. Sugar EA, Jabs DA, Ahuja A, et al. Incidence of cytomegalovirus retinitis in the era of highly active antiretroviral therapy. Am J Ophthalmol 2012;153:1016-1024 e1015.

19. Jabs DA. Cytomegalovirus retinitis and the acquired immunodeficiency syndrome--bench to bedside: LXVII Edward Jackson Memorial Lecture. Am J Ophthalmol 2011;151:198-216 e191.
20. Thorne JE, Jabs DA, Kempen JH, et al. Incidence of and risk factors for visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. Ophthalmology 2006;113:1432-1440.
21. Lynn WA, Lightman S. Syphilis and HIV: a dangerous combination. Lancet Infect Dis 2004;4:456-466.
22. Mathew RG, Goh BT, Westcott MC. British Ocular Syphilis Study (BOSS): 2-year national surveillance study of intraocular inflammation secondary to ocular syphilis. Invest Ophthalmol Vis Sci 2014;55:5394-5400.
23. Tran TH, Cassoux N, Bodaghi B, et al. Syphilitic uveitis in patients infected with human immunodeficiency virus. Graefes Arch Clin Exp Ophthalmol 2005;243:863-869.
24. Wickremasinghe S, Ling C, Stawell R, et al. Syphilitic punctate inner retinitis in immunocompetent gay men. Ophthalmology 2009;116:1195-1200.
25. Smith JR, Cunningham ET, Jr. Atypical presentations of ocular toxoplasmosis. Curr Opin Ophthalmol 2002;13:387-392.
26. Babu RB, Sudharshan S, Kumarasamy N, et al. Ocular tuberculosis in acquired immunodeficiency syndrome. Am J Ophthalmol 2006;142:413-418.
27. Hodge WG, Seiff SR, Margolis TP. Ocular opportunistic infection incidences among patients who are HIV positive compared to patients who are HIV negative. Ophthalmology 1998;105:895-900.

28. Richards JC, Maartens G, Davidse AJ. Course and complications of varicella zoster ophthalmicus in a high HIV seroprevalence population (Cape Town, South Africa). Eye 2009;23:376-381.

29. Gore DM, Gore SK, Visser L. Progressive outer retinal necrosis: outcomes in the intravitreal era. Arch Ophthalmol 2012;130:700-706.

30. Levinson RD, Vann R, Davis JL, et al. Chronic multifocal retinal infiltrates in patients infected with human immunodeficiency virus. Am J Ophthalmol 1998;125:312-324.

31. Kunavisarut P, Sirirungsi W, Pathanapitoon K, et al. Clinical manifestations of human immunodeficiency virus-induced uveitis. Ophthalmology 2012;119:1455-1459.