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Volume 4 | Issue 1 Article 5

2024

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Uveitis is a rare inflammatory disease with a prevalence of around 38 per 100,000 people and is the overall 5th leading cause of blindness in the developed world.[1,2] Uveitis is most commonly found in patients younger than 40 years of age, but it can occur in any age group with an etiology that varies within each age demographic.[1,3] While the etiology of certain forms of uveitis are not fully understood, there are some that are autoimmune in nature and others that are associated with systemic diseases such as sarcoidosis.[4] Uveitis may be inflammatory or infectious. It may affect various locations of the eye and present as anterior uveitis, intermediate uveitis (vitritis), posterior uveitis (including retinitis and chorioretinitis), or pan uveitis (in which there is diffuse intraocular involvement).[1] Generally, with early detection and treatment, most forms of uveitis can be controlled, and vision loss can be prevented.[2,3]

Among infectious causes of uveitis, cytomegalovirus (CMV) may cause either anterior uveitis or, more commonly, posterior uveitis (CMV retinitis).[5,6] CMV is a ubiquitous herpes virus that can impact various organ systems, such as the eye and GI tract, and is spread via direct contact. Generally, 50% of the population harnesses antibodies to CMV, and while many adults are serologically positive for CMV, the progression to end-organ disease and resulting permanent damage, including retinitis, is limited to immunocompromised patients, including patients with AIDS, hereditary immunodeficiencies, and chemotherapy and other iatrogenic immunosuppressive drugs.[5] Maternal-fetal transmission may also occur.

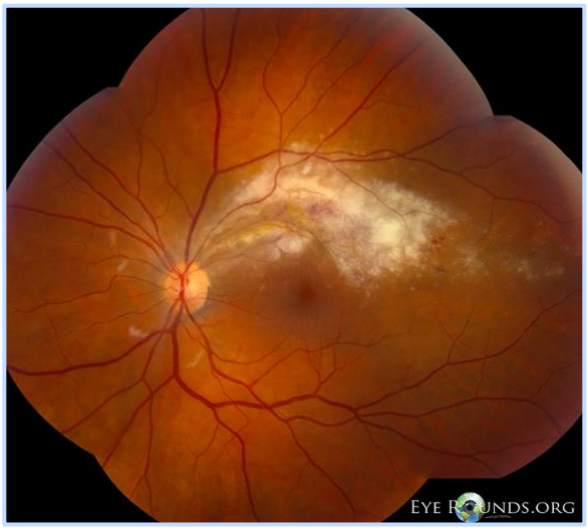

Figure 1: broad retinal whitening and intraretinal hemorrhages with cotton wool spots adjacent to the optic nerve consistent with CMV Retinitis.[16]

CMV itself employs a variety of mechanisms to evade the immune system of a healthy host and establish a latent infection. However, in immunodeficient patients, CMV can reactivate with triggers such as severe critical illness, including sepsis.[7,3] Prior to the onset of AIDS, CMV

retinitis was a rarely diagnosed condition. One manifestation of reactivation includes CMV retinitis. CMV retinitis is now considered an AIDS-defining illness in patients infected with human immunodeficiency virus (HIV).[8,9] The treatment options for both AIDS and CMV retinitis during the 1980s was limited. Prior to the introduction of disease-specific treatments, CMV retinitis concurrently occurred in approximately one-third of patients diagnosed with acquired immunodeficiency syndrome (AIDS) and accounted for over 90% of cases of HIV-related blindness.[10] In the 1990s, physicians associated with the American Academy of Ophthalmology suggested that due to its rising prevalence and concurrence with HIV, patients with HIV and CD4 counts below 50 cells/mm^3 should regularly screen for CMV retinitis.[6]

Early CMV retinitis presents with spots that may resemble cotton wool spots on the retina, although spots larger than 750 µm should raise concern for possible CMV retinitis. Three sometimes overlapping patterns of lesions have been described: a granular pattern, a fulminant/hemorrhagic appearance, or "frosted branch" angiitis.[6] When more than 25% of the retina becomes involved, there is a substantially increased risk for a rhegmatogenous retinal detachment.[6]

Dr. James P. Dunn taught in the Ocular Immunology Division at Johns Hopkins' Wilmer Eye Institute as an assistant professor during the 1990s. He encountered numerous patients with CMV retinitis, peaking at 80 patients in 1992 alone. At the time, treatment options were limited, and patients with CMV retinitis had a median survival of just 8-12 months due to other AIDS-related complications. Affected patients confronted difficult realities as he describes that most would initially present with visually significant disease. Counseling patients on the immense decisions they faced was a major component of his work. Some patients were not interested in the often toxic therapeutic interventions of intravenous ganciclovir or foscarnet to maintain their vision while others would be willing to entertain any form of therapy to prevent further vision loss. These decisions included collaboration with a medical team consisting of physicians from numerous specialties highlighting the complexity of widespread infliction upon the human body from systemic illness. Dr. Dunn's experience as a provider during the AIDS epidemic, especially through the lens of CMV retinitis, underscores the myriad of influences impacting drug development during a major health crisis.

Therapeutic drug development during the ongoing AIDS crisis was affected by the rising prevalence of CMV retinitis. For instance, ganciclovir is a therapeutic agent that, in its active form, can both inhibit viral DNA polymerase and be integrated into growing DNA as a false base. Its integration leads to transcription of either a mutant chain of DNA or termination of DNA elongation, ultimately

Figure 2: Dr. James P. Dunn, courtesy of Roger Barone, Wills Eye.

leading to inhibition of viral replication.[11] With the surge of cases, copious studies for CMV retinitis therapy like intravenous ganciclovir were conducted, eventually leading to its licensure as the mainstay treatment in 1989.[11] Ganciclovir was a potent medicine commonly prescribed to treat CMV but held the risk of serious myelosuppressive complications such as neutropenia and thrombocytopenia when administered systemically.[12] Due to these harmful effects, alternative routes of administration were studied to elicit the method of delivery with the lowest risk profile. These explorations analyzed the delivery of ganciclovir intraocularly, orally, and even through intraocular device implantation. The ganciclovir implant was an effective therapeutic option for unilateral CMV retinitis that enabled physicians to provide treatment directly to infected eyes for a prolonged period of time, an element that was missing with single intraocular doses of ganciclovir.[13] Implant administration required intraocular surgery for precise placement to allow directed release of ganciclovir over a period of 6-8 months.[13]

Cases of CMV retinitis peaked in the early 1990s and decreased dramatically by roughly 80% in patients with AIDS with the introduction and widespread availability of highly active

antiretroviral therapy (HAART) for HIV in 1996.[14] HAART therapy, also known as antiretroviral therapy (ART), consists of six main drug classes of ART and each targets different phases of the HIV life cycle. These classes include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), fusion inhibitors (FIs), and chemokine receptor antagonists (CCR5 antagonists).[15]

Following the breakthrough of HAART, the impetus to discover novel medicines to treat CMV retinitis, specifically, decreased due to the declining incidence of patients with HIV/AIDS and thus CMV retinitis. Some therapies utilized in the early 90s for CMV treatment were eventually discontinued. The ganciclovir implant, for example, was taken off the market in 2013 not from adverse effects but from declining sales as widespread use of HAART led to a dramatically reduced incidence of CMV retinitis. There is, therefore, a relative decline in understanding among medical students, residents, and physicians over the last 25-30 years of how CMV retinitis presents clinically. Ophthalmologists and researchers are not encountering cases of CMV retinitis as frequently as the incidence of this disease has decreased significantly. Thus, medical personnel and professionals are not seeing this condition as regularly to recognize its tell-tale signs.

Nonetheless, CMV retinitis can still occur despite the decrease in prevalence of AIDS in the current day. Patients with severe immunosuppression (patients currently receiving chemotherapy or immunomodulators) are at a continued risk for CMV retinitis as CMV can reactivate in the presence of certain risk factors as with other opportunistic infections.[6]

Overall, Dr. Dunn's experience as a uveitis specialist, working on the front lines during the AIDS epidemic, is inspiring. His final reminders to students emphasize the critical role physicians have in their patients' lives and the value of centering care around compassion and understanding.

References

1. Cao J. (2022, July 28). Understanding uveitis: A vision-threatening but treatable eye disease. Eyes and Vision. https://utswmed.org/medblog/uveitis-eye-inflammation/#:~:text=Uveitis%20is%20a%20rare%20inflammatory,patients%20in%20the%20Western%20world.

2. U.S. Department of Health and Human Services. (2023, November 15). Uveitis. National Eye Institute. https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/uveitis#:~:text=Uveitis%20is%20inflammation%20inside%20your,healthy%20tissue%20in%20your%20eyes.

3. Joltikov KA, Lobo-Chan AM. Epidemiology and Risk Factors in Non-infectious Uveitis: A Systematic Review. Front Med (Lausanne). 2021 Sep

10;8:695904. doi: 10.3389/fmed.2021.695904. PMID: 34568364; PMCID: PMC8461013.
4. Egwuagu CE, Alaheem SA, Mbanefo EC. Uveitis: Molecular pathogenesis and emerging therapies. Frontiers in Immunology. 2021 April 30; 12:623725. doi: 10.3389/fimmu.2021.623725.
5. Fabozzi L, Testi I, De Benito-Llopis L, Pavesio C. Cytomegalovirus anterior uveitis and occlusive retinal vasculitis without retinitis in a patient on immunomodulatory therapy. J Ophthalmic Inflamm Infect. 2023 Aug 4;13(1):34. doi: 10.1186/s12348-023-00356-z. PMID: 37540447; PMCID: PMC10403449.
6. American Academy of Ophthalmology. (n.d.). CMV Retinitis. EyeWiki. https://eyewiki.aao.org/CMV_Retinitis#:~:text=Patients%20with%20CD4%20counts%20less,active%20retinitis%20is%20typically%20asymptomatic.
7. Jabs DA. Cytomegalovirus retinitis and the acquired immunodeficiency syndrome--bench to bedside: LXVII Edward Jackson Memorial Lecture. Am J Ophthalmol. 2011 Feb;151(2):198-216.e1. doi: 10.1016/j.ajo.2010.10.018. Epub 2010 Dec 18. PMID: 21168815; PMCID: PMC3057105.
8. Perello R, Vergara A, Monclus E, Jimenez S, Montero M, Saubi N, Moreno A, Eto Y, Inciarte A, Mallolas J, Martínez E, Marcos MA. Cytomegalovirus infection in HIV-infected patients in the era of combination antiretroviral therapy. BMC Infect Dis. 2019 Dec 4;19(1):1030. doi: 10.1186/s12879-019-4643-6. PMID: 31801482; PMCID: PMC6894188.
9. Imlay H, Limaye AP. Current Understanding of Cytomegalovirus Reactivation in Critical Illness. J Infect Dis. 2020 Mar 5;221(Suppl 1):S94-S102. doi: 10.1093/infdis/jiz638. PMID: 32134490; PMCID: PMC7057786.
10. Heiden D, Ford N, Wilson D, Rodriguez WR, Margolis T, Janssens B, Bedelu M, Tun N, Goemaere E, Saranchuk P, Sabapathy K, Smithuis F, Luyirika E, Drew WL. Cytomegalovirus retinitis: the neglected disease of the AIDS pandemic. PLoS Med. 2007 Dec;4(12):e334. doi: 10.1371/journal.pmed.0040334. PMID: 18052600; PMCID: PMC2100142.
11. Tseng A, Foisy M. The role of ganciclovir for the management of cytomegalovirus retinitis in HIV patients: Pharmacological review and update on new developments. Can J Infect Dis. 1996 May;7(3):183-94. doi: 10.1155/1996/780831. PMID: 22514437; PMCID: PMC3327402.
12. Mills, J., Mark A. Jacobson, O'Donnell, J. J., Donna Cederberg, & Gary N. Holland. (1988). Treatment of Cytomegalovirus Retinitis in Patients with AIDS. Reviews of Infectious Diseases, 10, S522–S531. http://www.jstor.org/stable/4454632
13. Martin DF, Parks DJ, Mellow SD, Ferris FL, Walton RC, Remaley NA, Chew EY, Ashton P, Davis MD, Nussenblatt RB. Treatment of cytomegalovirus retinitis with an intraocular sustained-release ganciclovir implant. A randomized controlled clinical trial. Arch Ophthalmol. 1994 Dec;112(12):1531-9. doi: 10.1001/archopht.1994.01090240037023. PMID: 7993207.
14. Ude IN, Yeh S, & Shantha JG. (2022). Cytomegalovirus retinitis in the highly active anti-retroviral therapy era. Annals of Eye Science, 7, 5–5. https://doi.org/10.21037/aes-21-18
15. Eggleton JS, Nagalli S. Highly Active Antiretroviral Therapy (HAART) [Updated 2023 Jul 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554533/
16. Atlas Entry - Cytomegalovirus (CMV) Retinitis [Internet]. [cited 2024 Mar 9]. Available from: https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/cmv-retinitis/index.htm