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Case Discussions

National HIV Curriculum Podcast

CMV Retinitis: Evaluation and Management

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National HIV Curriculum Podcast Editors Dr. Jehan Budak and Dr. Aley Kalapila discuss possible causes of visual changes in advanced HIV and the diagnosis and management of CMV retinitis in people with HIV.

Topics:

- OIs and HIV
- CMV
- Retinitis
- advanced HIV

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Transcript

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introduction**[00:00] Introduction**

Hello everyone. I'm Dr. Jehan Budak from the University of Washington in Seattle, and welcome to the National HIV Curriculum Podcast. This podcast is intended for health care professionals who are interested in learning more about the diagnosis, management, and prevention of HIV. I'm back with my colleague, Aley Kalapila, an ID physician at Emory University in Atlanta. Hi Aley!

Dr. Kalapila

Hi Jehan. Hi everyone listening, looking forward to this new episode.

Dr. Budak

And today, we'll be talking about a case of a patient with advanced HIV who has ocular complaints. The case is that of a 33-year-old patient with HIV with last CD4 count of 340 and viral load 50,000 who had been out of care for five years. He's had inconsistent ART [antiretroviral therapy] adherence the whole time he's had HIV, and states that he was doing well until approximately three months ago when he started feeling more tired. When he re-established care at this clinic visit, he was initiated on ART and sent out with close follow-up, but after he left the clinic, his labs resulted and showed a CD4 count of 9. So a few days later, his primary care doctor called to check in on him, and during that conversation, the patient shared that he was developing eye pain. He also stated that he had blurry vision and floaters for the last few months.

differential-diagnosis**[01:18] Differential Diagnosis**

Dr. Budak

So, I think that this is a good time to pause and ask you, Aley, to take us through a differential diagnosis for visual changes in a person with advanced HIV.

Dr. Kalapila

Sure, so, for a patient who has visual symptoms and who has HIV, probably the two most common pathogens that I would think about would be syphilis and cytomegalovirus, which we often say as CMV or abbreviate as CMV. Now, when the T cell count for the patient is less than 50, CMV really kind of floats to the top of my list. Now, visual changes can occur in any ocular compartment, and it's really hard to know what exactly is happening to the patient pathophysiologically without an actual exam, but to make sure we're not missing anything as far as differential diagnosis is concerned, let's actually kind of walk through this systematically. So, let's first start with bacterial causes, so, of course, syphilis. Now, syphilis can affect any structure in the eye, from the front all the way to the back. The classic presentation that we typically associate with syphilis is uveitis, particularly anterior uveitis. You can see a panuveitis with syphilis, as well. Now, the other big bacterial etiology that I think about for patients living with HIV, aside from sort of the typical bacterial pathogens like staph or strep that you might see maybe with endophthalmitis, the other bacterial etiology that I would think about would be tuberculosis. And, now, TB uveitis, or sort of TB-itises I guess, is very difficult diagnosis to make primarily because it is a paucibacillary disease. So I think of TB affecting the eye not as the bug driving problems within the eye but rather the immune system's reaction to TB causing problems with the eye.

The next bucket that I think about is viral, and of course CMV is the biggest viral infection that we would think about that typically causes retinitis in this patient population. But, other herpesviruses, particularly VZV, or

varicella zoster virus, and herpes simplex virus, or HSV, can also cause eye problems in patients who are immunocompromised, as well. Now, with VZV, we often see a retinal necrosis, and with HSV, we can see a keratitis.

The next bucket that we would think about would be fungal, which is less likely in this patient population. The fungi that we think about as causing problems in people living with HIV would include bugs like cryptococcus or histoplasmosis, and I don't always think of them as classically affecting the eye.

And then, of course, we have our protozoal bucket, and this is, of course, toxoplasmosis—it's a big one. Now, we've discussed in other episodes of this podcast that the classic presentation of toxoplasmosis, or toxo, in advanced HIV is encephalitis, but toxo-retinitis is a thing, and it can actually occur in patients living with HIV.

Dr. Budak

Thanks, Aley. So, yeah, it sounds like, okay, syphilis, CMV mean big things that we would think about in this patient. I think that there are also AIDS-associated malignancies that can affect the eye, but those are more rare. And, I don't know about you, but I'd think that immune reconstitution inflammatory syndrome, or IRIS, which we'll say from here on out), would be very unlikely in this specific situation because he has only been on ART for just a few days.

Dr. Kalapila

Totally agree. To clarify, the IRIS that you're referring to is called an *unmasking* IRIS, so this is when the patient has an occult underlying process, and this could be either an AIDS-associated infection or an AIDS-associated malignancy, and it is not picked up on initially when the patient is first evaluated by the clinician. So, the patient has an occult process, you as a clinician don't necessarily clue in that the patient might have something going on underlying, you start the patient on ART, and all of a sudden, they have immune reconstitution a couple of weeks to months later and now their symptoms of the original occult process that they have are now flaring. You've now unmasked whatever was happening in the first place, and this is called an unmasking IRIS, or unmasking immune reconstitution syndrome.

Dr. Budak

Perfect! Totally agree, Aley, and, again, we don't think that's what's going on in this case because it's just been a few days that he's been on ART.

initial-evaluation**[05:35] Initial Evaluation**

Dr. Budak

So, now, back to the case. What did you do after hearing his history?

Dr. Kalapila

So, regardless of his disposition, be it the clinic or emergency room, the bottom line is that he needs an eye exam as soon as possible, and he may need to have intravitreal injections if the diagnosis of CMV retinitis is confirmed. Now, this can be hard to coordinate as an outpatient, and so in those situations, I often will see patients admitted to the hospital. In this particular case, because of social barriers and for access to care, we actually did choose to directly admit him from our clinic to the inpatient service, we have the ability to do that, for an urgent optho [ophthalmologic] exam because our concern for CMV retinitis was very high. Now, around the time of the hospitalization, we also obtained baseline labs, and these included a CBC, complete blood count, and a comprehensive metabolic panel because, as you know, most of our antimicrobials can affect kidney and liver function as well as cause cytopenias, so it's always good to have a baseline to know where you're starting from. And then, of course, because syphilis is on our differential like we already

discussed, I also sent off a syphilis serologic test, which ended up being negative. Once the patient was admitted, optho was able to come in immediately and evaluate him, as well.

Dr. Budak

Yeah, as you said, Aley, his initial evaluation can be coordinated as an outpatient, but it all depends on access to care. So sometimes the frequency of the visits makes it difficult for a patient to come back daily, in which a hospitalization may make it easier for them in the initial stages of the disease. And also, the severity of the disease impacts the frequency of the treatments necessary, which may be difficult for a patient to come back and forth almost on a daily basis. So, all this to say, there's no right way to go about this, but often hospitalization is necessary and helpful.

Dr. Budak

In your case, optho saw the patient and noted that he had an area of hemorrhage and retinal whitening in the left eye, which was concerning for CMV retinitis. They did an intravitreal aspiration and sent it off for PCR [polymerase chain reaction] and testing for CMV, HSV, VZV, and toxo. And, so, while that's pending, what did you do?

Dr. Kalapila

So, in discussion with the ophthalmologists who were involved with the case, they told us that they were very concerned for CMV, and so given this, we opted to start our empiric treatment with intravenous ganciclovir, which also conveniently happens to treat other herpesviruses, while we're waiting for those PCR test results to come back. And because the concern for CMV retinitis was so high optho, also initiated intravitreal foscarnet and ganciclovir, even prior to the PCR test results returning.

basis-cmv-diagnosis**[08:24] Basis for CMV Diagnosis**

Dr. Budak

And that brings up a great point, that the diagnosis of CMV retinitis is made based on clinical presentation. The DHHS Opportunistic Infection Guidelines state that CMV retinitis is usually diagnosed based on "recognition of classic retinal changes observed on a dilated fundoscopic exam performed by an experienced ophthalmologist." And they also state that a clinical diagnosis made in that situation has a 95% positive predictive value. So, all this to say, definitely trust the eye doctors.

Dr. Kalapila

Exactly. The DHHS makes a very good point of saying you need to have a good eye exam by an experienced ophthalmologist and not an experienced ID doctor. So, the intravitreal PCR testing also is not necessarily required in my clinical experience, but our ophthalmologists typically will go ahead and do it. They do send off intravitreal fluid for PCR testing, and usually, when they send it off for PCR testing, particularly in patients with advanced HIV who present with these findings, they will send it off for CMV and the other herpesviruses, HSV and VZV, and then also toxo. And, of course, they do this because you don't really want to miss other co-existing diagnoses. Since we know that this patient is so very immunocompromised, he could have multiple opportunistic infections happening both at the same time. And, so this is why the PCR testing can be important as well. And I think the other important point that I should probably also mention here is the value of serum CMV PCR testing. Now, this is actually not recommended by the Opportunistic Infections Guidelines because they have a very poor positive predictive value in people with advanced HIV.

Dr. Budak

Yes, the guidelines state that a negative vitreal PCR does not rule out a diagnosis of CMV retinitis. So, with

CMV GI [gastrointestinal] end-organ disease, like with CMV colitis, for example, but any end-organ diseases, the gold standard is biopsy, where you would expect typically to see inclusion bodies on pathology. But for ocular disease, as we mentioned, the diagnosis is based on clinical findings and the intravitreal PCR testing, which again, might be negative at times, but again, clinical diagnosis because it's really hard to biopsy an eyeball and not recommended.

cmv-principles-treatment**[10:48] CMV and Principles of Treatment**

Dr. Budak

Let's actually take this moment to talk a little bit about CMV, which is a herpesvirus that most of us have been exposed to. Once we've been exposed, it enters a period of latency and can reactivate in the setting of illness, even in someone who is immunocompetent, but should not cause end-organ damage. Whereas, in the setting of immunocompromise, CMV can cause tissue-invasive disease, and in people with HIV, we tend to see this when the CD4 count is less than 50 and the individual is off ART. And in advanced HIV, the most common location we see end-organ damage is the eye, but we can also see it in the GI tract, CNS [central nervous system], and lungs, though those are less likely. And when dealing with ocular anatomy, which I think is just confusing at baseline, I typically think of CMV affecting both. There's the anterior segment and the posterior segment. Anterior segment causes disease in immunocompetent individuals. Posterior segment CMV is seen in immunocompromised individuals, and that's where we tend to see that CMV retinitis, like in people with HIV.

So, now that we've talked a little bit about CMV in general, the diagnosis of CMV, Aley, can you take us through the principles of treatment?

Dr. Kalapila

The first thing for treatment of CMV retinitis, much like many other opportunistic infections, is done in different phases. The initial phase is called the induction phase. So this is when we use intensive antimicrobial and, in this case, antiviral therapy, and the main goal for induction is to actually lower the organism burden. Now, this has been followed by a maintenance phase, which is a little bit less intensive, and typically, this is continued for a more prolonged period of time until the patient has no evidence of disease and has also managed to achieve immune reconstitution on antiretroviral therapy.

Now, let's break that down a little bit more. First, let's talk about induction. So, the first-line medication we use for CMV retinitis is either ganciclovir, and this is administered intravenously, or oral valganciclovir. We have other IV options. They are cidofovir and foscarnet, which can be effective, but due to toxicity, particularly kidney toxicity, we do not use them for first-line treatment. So, really, our first option for induction therapy are IV ganciclovir or oral valganciclovir. Now, the good thing is that oral valganciclovir is very, very bioavailable, and actually, there was a study about this that I think, Jehan, you're going to take us through.

iv-vs-oral-therapy**[13:19] IV vs Oral Therapy**

Dr. Budak

You know how much I love talking about papers and trials! So, this was the 2002 *New England Journal of Medicine*that published a paper by Martin et al., and this was a randomized trial of 160 patients with AIDS and CMV retinitis who were randomized 1:1 to either IV ganciclovir or oral valganciclovir for induction therapy. And let's skip over most of the details, but the conclusion was that oral valganciclovir was found to be as effective as IV ganciclovir for induction therapy. So, I think, based on this paper, a lot of us feel comfortable with starting oral therapy.

Dr. Kalapila

Agreed. That paper was very informative and super helpful. And it definitely makes me more comfortable in wanting to initiate oral therapy, knowing that it is as bioavailable as intravenous therapy. Now, that being said, I will say that in this case, or in any case really, I will always defer to the ophthalmologist, because they may want to start initially with parenteral therapy if they feel like the exam shows some very severe retinal disease. And, by that they typically say that the lesions that they're seeing are sight-threatening lesions. So, in those cases, IV ganciclovir would be what we want to start with up front. And, again, like I said before, we always have this discussion with ophtho, and they will then help us determine at what point they feel comfortable switching back to oral or switching to oral therapy if we haven't used oral therapy up front. They will continue to do eye exams on a regular basis, let us know if the patient is having a good clinical response, and that's usually when they'll signal to us and say, "Okay, you can now switch from IV therapy to oral." Usually this is a time at which we can discharge the patient to home safely if they're in the hospital getting IV therapy, as well. Now, if intravitreal injections are used up front, the ophthalmologists will continue to give the injections on a weekly basis until the lesions become inactive. This, of course, can be coordinated in an outpatient clinic once the patient is discharged from the hospital.

length-tx-phases**[15:38] Length of Tx Phases**

Dr. Budak

Okay, so we've discussed the nuances between IV and oral therapy, and we are still in the induction phase of treatment. Can you take us through about how long that lasts?

Dr. Kalapila

So, the induction period usually lasts for about 14-21 days, and again, the duration is determined by response to therapy based on optho's retinal exam. I usually will talk to the ophthalmologist to determine when they feel that the patient can be safely discharged home. And, once the patient's discharged home, I'll obviously then switch to oral antivirals. In this case, oral valganciclovir. Our patient was transitioned after one week of IV ganciclovir to oral valganciclovir, but we maintained him at induction dosing, again, because of the recommendation by ophthalmology and because, like we said, the duration of induction dosing is that 14-21 days. The dose for oral valganciclovir at induction dose, so higher dosing for antiviral drugs for induction, is 900 mg twice a day, and then we got him scheduled for follow-up as an outpatient in optho clinic. I continued to discuss with optho regarding when they think the patient has completed an adequate course of induction therapy. In this particular case, the ophthalmologists wanted a 21-day induction course, which we did, given the severity of his retinal disease. And then, after those 21 days, we then decreased the dose of his antivirals to maintenance dosing, and this was 900 mg of oral valganciclovir, dosed once a day, and this is maintenance therapy.

Now, for patients who are on maintenance therapy, they're going to remain on this, like I said, for a longer period of time, typically at least 3-6 months of antiviral therapy. They're going to have continual evaluations by optho, so you have to continue the oral antivirals until they have no active retinal lesions. You're going to continue it until they have T cell counts greater than 100 for about 3-6 months in response to oral ART. Now, the decision to discontinue maintenance therapy, again, should always be done in discussion with ophthalmology.

Dr. Budak

So that's definitely a theme here, that everything regarding CMV retinitis management is done in coordination with ophthalmology.

art-start--thorough-review-systems**[17:50] ART Start & Thorough Review of Systems**

Dr. Budak

So, now, to switch gears a bit, what about starting ART?

Dr. Kalapila

I would start ART as soon as possible. The OI Guidelines do state that most experts would initiate ART no later than two weeks after starting anti-CMV therapy.

Dr. Budak

And, Aley, how much do you worry about IRIS with CMV retinitis?

Dr. Kalapila

Yeah, it's something to keep an eye out for, both literally and figuratively, because it can happen. And specifically, in this case, we want to watch out for paradoxical IRIS. So this is where we're referring to a previously treated infection, so in this case, this patient had CMV that's being treated and then it's starting to get worse once you start the antiretroviral therapy. But I worry a little bit less about paradoxical IRIS because I know that the patient has already received up front antiviral therapy for his CMV disease.

This is different from unmasking IRIS, which we touched on a little bit earlier, because unmasking IRIS is, like I said, when a patient presents to you, they have occult, or they may not have symptoms at all of an undiagnosed opportunistic infection or malignancy, and then you start them on ART, and now you've unmasked their occult process and they have a flare-up of their underlying disease. Now, I think the point here to make is that when evaluating a patient in your clinic and you're about to start them on antiretroviral therapy, and their T cell count is low, it's extremely important to do a very thorough review of systems because patients can often minimize symptoms of OIs or AIDS-associated malignancies. So, in the case of CMV retinitis, I've had patients complain of floaters or they'll say, "I need glasses." They really minimize their complaints, especially because most of these symptoms happen very gradually. They don't have an acute presentation. And also remember that you really need an immune system to have profound symptoms and these patients have no immune system at all. So, you have to have a very high level of suspicion that even with their minimal complaints, you should think, "Oh, there might actually be something going on here, and I have to have them evaluated by an ophthalmologist." I have a very low threshold to refer patients for an eye exam even if I feel like they have very subtle eye complaints as well, because if you don't refer them and they have undiagnosed CMV eye disease, if you give them ART, they can have a terrible unmasking IRIS, and they can actually have extensive inflammation and maybe even vision loss. So, again, an eye exam is an easy thing to do, it's an easy thing to refer a patient, it's noninvasive. Do a thorough review of systems when you're evaluating patients, and you're about to start them on ART and then have a low threshold to refer them to ophthalmology if they have any subtle visual complaints

Dr. Budak

Great points, Aley. I think always a good reminder about the importance of a thorough review of systems, which I admit sometimes I will, especially in clinic, accidentally gloss over some of them, but again, great reminder to continue to do those and be vigilant, especially when starting ART in someone who has a low CD4 count. And then to your point about having a low threshold for eye exam, at one of the HIV clinics I used to work at, we had to automatically consult ophtho for a baseline eye exam if the person had a CD4 count less than 50, and if they were asymptomatic, it was just a baseline eye exam. And in fact, the guidelines actually have a CIII recommendation that some clinicians obtain a baseline ophtho exam for people with HIV with a CD4 count less than 100.

Dr. Kalapila

Yes, you know, I see a fair amount of advanced HIV in Atlanta, and my practice is to typically have a very, very low threshold, as I mentioned earlier, for a baseline ophtho exam or optho evaluation, especially in

patients with CD4 counts that are less than 100, even if they're asymptomatic.

Dr. Budak

So, I think, whatever one's practice is regarding a baseline asymptomatic eye exam, it is important to remember that there can be a fair amount of asymptomatic early CMV retinitis.

summary**[21:58] Summary**

Dr. Budak

And so, with that in mind, I'd like to wrap up this episode with a few summary points based on what Aley was saying, so:

- CMV disease in people with HIV typically occurs when T cell counts are less than 50 and is due to reactivation of latent infection in the setting of advanced immunosuppression and most commonly affects the retina.
- The diagnosis of CMV retinitis, as we talked about, is made on a dilated fundoscopic optho exam, though intravitreal PCR testing can be used to confirm the diagnosis and to evaluate for other possible pathogens.
- As Aley talked about, treatment consists of two phases: a 14- to 21-day induction course with high-dose antivirals, which we can do either parenterally or orally, with the route depending on the severity of the retinitis and what optho recommends, followed by maintenance therapy, which is lower doses of the oral antivirals. And oftentimes, optho might do an intravitreal injection concurrently with the systemic antivirals in the induction phase.
- ART can be started as soon as possible, but as we know in the guidelines, they say at least within two weeks of starting anti-CMV treatment.
- And the last key point, in case we haven't emphasized it enough already, is that we need to coordinate and communicate with ophthalmology when managing CMV retinitis.

So, that brings us to the end of this episode. Thank you again, Aley!

Dr. Kalapila

Thanks, Jehan. I'll see you at our next podcast episode.

Dr. Budak

Sounds great! Thanks. Bye, everyone.

credits**[23:29] Credits**

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