

## Challenges in Cytomegalovirus (Cmv) Retinitis Management

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### ABSTRACT

**Introduction:** HIV infection can manifest in a variety of ways in and around the eyes and it is most commonly due to retinal microvasculopathy, neoplasm and also opportunistic infection. Those usually occur associated with a significantly reduced CD4 T-cell counts. In this era of Highly Active Anti Retroviral Therapy (HAART) has caused a major decreasing of the ocular involvement prevalence itself.

**Case report:** A 31 year-old-male came with blurred vision on the right eye, which has started 3 years ago and slowly worsened. Central scotoma also presented previously. Patient was an HIV-AIDS, that placed him on HAART. CD4+ T-lymphocyte count was 3 cells/mm<sup>3</sup>. The initial visual acuity was light perception and fundus examination showed Roth spots, massive exudates and hemorrhages covering the optic disc and decreased foveal reflex. Laboratory examination revealed positive Rubella and anti-CMV immunoglobulin-G (IgG). He also suffered from lung tuberculosis and took tuberculosis medication regularly. Patient was diagnosed with Cytomegalovirus (CMV) retinitis based on history of illness, fundus examination as well as laboratory testing and given oral induction valganciclovir 900 mg once daily for 3 weeks followed by maintenance dosage.

**Result:** After valganciclovir induction, there was significant changes with decreased peripapillary exudates, hemorrhages and vasculitis, but the optic disc appeared pale. The patient also had bicytopenia due to valganciclovir therapy that complicate his condition and passed away after 3 months follow up.

**Conclusion:** CMV retinitis is reported to occur in patient with extreme CD4 count usually less than 50 cells/mm<sup>3</sup>. The sooner of proper treatment would likely following better outcome. Making diagnosis of immunosuppressed patient with ocular manifestations was challenging so that comprehensive eye examination in HIV-infected individuals should be conducted. Oral valganciclovir could give satisfactory response to decrease the progression of retinitis but risk of blindness may still occur.

**Keywords:** cytomegalovirus, CMV retinitis, valganciclovir, HIV-AIDS, CD4+ T-lymphocyte

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### INTRODUCTION

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Human immunodeficiency virus (HIV) remains a major public health problem with 56,000 new HIV infections per year in the United States.<sup>1</sup> In Indonesia, HIV/AIDS reported case was 3,679 in 2016.<sup>2</sup> It is estimated that about 70 to 80% of adult HIV/AIDS patients will experience ocular complication during their illness.<sup>3</sup> The majority

of ocular involvement in HIV is HIV retinopathy and Cytomegalovirus (CMV) retinitis. HIV retinopathy is a non-infectious microvascular disorder characterized by cotton wool spots, microaneurysms, retinal hemorrhages, Roth spots and telangiectatic vascular changes.<sup>4</sup>

The most common manifestation of this disorder is cotton wool spots. Unlike infective lesion, cotton wool spot in HIV retinopathy are transient, not visually threatening and tend to disappear within 6-12 weeks.<sup>5</sup> Retinal hemorrhages are seen less frequently in approximately 30% of patients with advanced HIV/AIDS.<sup>6</sup> It may appear as flame-shaped areas when they affect the nerve fiber layer and as dot-and-blot patterns when they affect the deeper layers of the retina.<sup>7</sup> It can be differentiated from CMV retinitis by the presence of fewer hemorrhages and the absence of subtle iritis or vitritis.

CMV retinitis is the most common ocular opportunistic infection that potentially blinding of patients with HIV-AIDS. This disease occurred in up to one-third of HIV-infected patients before the invention of highly active anti retroviral therapy (HAART) and significantly associated with CD4+ T-lymphocyte cell count <50 cells/mm<sup>3</sup>.<sup>8,9</sup> The incidence of CMV retinitis in the post-HAART era is estimated to be at most 5.6 cases/100 persons/year.<sup>10</sup> CMV retinitis is characterized by typical white, crumbly areas of retinal necrosis and hemorrhage which is sight threatening if originate in posterior pole. Cotton wool spot is an early manifestation of CMV retinitis.<sup>9</sup> The lesions tend to enlarge and coalesce over time, forming large, wedge-shaped areas of involvement.<sup>11</sup>

The clinical forms of CMV retinitis divided as typical form which appear as white spots with many hemorrhages, atypical form which appear as a zone of thinned retina and small dot infiltrate without hemorrhages, perivascular form or "frosted branch angiitis" and optic neuropathy which has the worst prognosis.<sup>12</sup> Patient with vision disturbance may have irreversible vision loss because of direct damage to the macula and optic nerve, retinal detachment even after CMV retinitis has resolved and immune recovery uveitis.<sup>13</sup> CMV retinitis can be treated with ganciclovir or foscarnet, administered systemically or intravitreally.<sup>14</sup> Another drug of choice is valganciclovir, an orally administered monovalent ester prodrug of ganciclovir. Induction therapy typically 900 mg once daily for 2-3 weeks followed by maintenance therapy 450 mg once daily.<sup>10</sup>

**CASE REPORT**

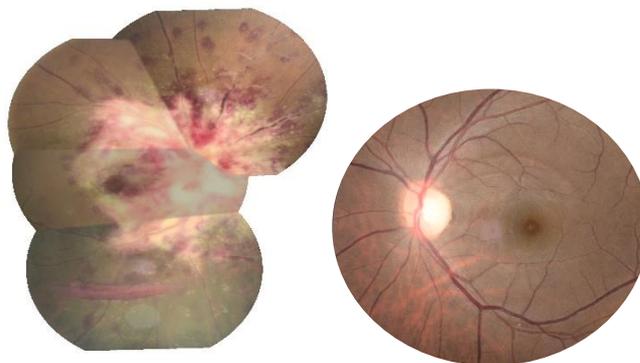
A 31-year-old man referred to the outpatient clinic with painless visual loss on the right eye since three years ago, started with black dot in the center of his vision, that slowly worsening by time. Patient had been diagnosed with HIV since 4 years and treated with highly active anti retroviral therapy (HAART) such as Emtricitabine/Tenofovir and Lopinavir/Ritonavir. This patient also suffered from lung tuberculosis and had taken anti-tuberculosis fixed-dose combinations (FDCs) for five months. Discrete painless

papulo-nodular lesions found over face and neck, assessed as pruritic papular eruption and molluscum contagiosum (Figure 1).



**Figure 1. Discrete papulonodular lesions (pruritic papular eruption and molluscum contagiosum)**

The visual acuity was light perception on the right eye with mid-dilated pupil, and relative afferent pupillary defect (RAPD) was present at presentation. There was no inflammatory sign on anterior segment. Funduscopy examination revealed massive soft exudates and hemorrhages in posterior pole covering the optic disc, Roth's spot, necrotic lesion due to vasculitis and also reduced foveal reflex (Figure 2). The left eye was within normal limit. Laboratory test showed low CD4 count of 3 cells/mm<sup>3</sup>, anemia 8.5 g/dl, positive IgG rubella and anti-CMV. Chest x-ray revealed infiltrates with suspicious of lung tuberculosis.



**Figure 2. Fundus photograph both eyes before oral valganciclovir therapy. Right eye showed massive soft exudates and hemorrhages in posterior pole**

The patient was diagnosed with cytomegalovirus (CMV) retinitis and treated with oral valganciclovir, 900 mg once daily for 3 weeks induction therapy and followed by 450 mg once daily for maintenance therapy. Funduscopy examination was done at the end of induction therapy, showed significant changes with decreased peripapillary exudates, hemorrhages and vasculitis, but the optic disc appeared pale (Figure 3).

Optical Coherence Tomography (OCT) examination showed macular thickening, intraretinal and subretinal fluid (Figure 4).

Shortly after the end of induction therapy, patient was admitted at Department of Internal Medicine ward due to chronic diarrhea and bicytopenia. Hemoglobin decreased to 6.5 g/dl and white blood cells (WBC) count was 1.430. He had to get PRC transfusion and at that time, considering his weak condition, Internal Medicine Department suggested to postpone valganciclovir maintenance therapy since it appeared to be the underlying cause of his bicytopenia. During hospitalized, visual acuity decreased to no light perception.

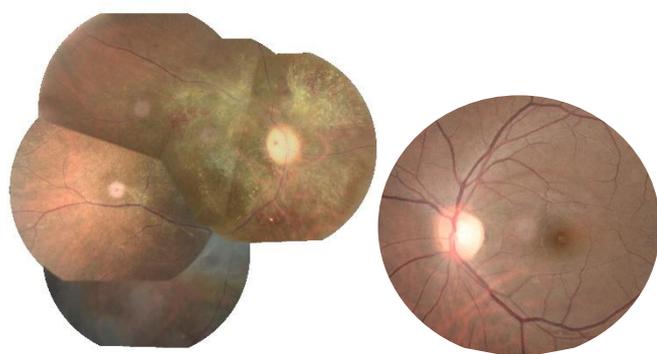


Figure 3. Fundus photograph both eyes after oral valganciclovir induction therapy. Right eye showed significant decreasing of exudates and hemorrhages

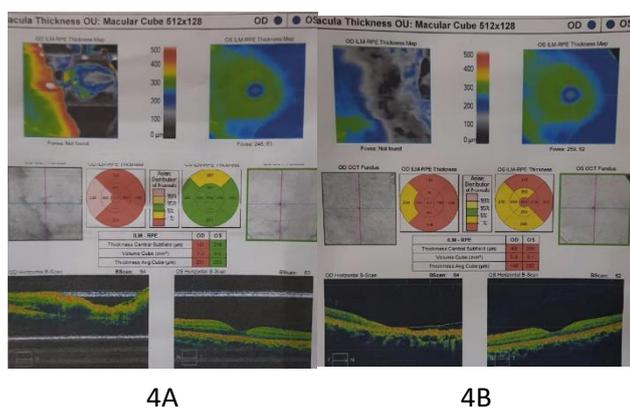


Figure 4. Macular OCT both eyes before valganciclovir induction therapy (4A) and after valganciclovir induction therapy (4B)

One week after, valganciclovir maintenance therapy was continued. During one week follow up, there was no changes in visual acuity, funduscopy showed a pale optic disc, necrotic lesion and decreased exudates with minimal hemorrhages. Patient passed away after 3 months evaluation with remained ocular condition.

**DISCUSSION**

HIV/AIDS is undoubtedly a multi systemic disease and ocular involvement occurs in up to 70% of cases during the natural history of infection. Ocular manifestations of HIV-associated spectrum are very broad and extend from a simple blepharitis to blindness.<sup>12</sup> The two most common posterior segment ocular manifestations of HIV/AIDS are HIV retinopathy and cytomegalovirus (CMV) retinitis. In this case, the patient complained of gradually painless visual loss with central scotoma and also massive exudates and hemorrhages on funduscopy. HIV retinopathy itself is an occlusive microangiopathy,<sup>15</sup> which presents as cotton wool spots, microaneurysms and retinal hemorrhages.

However, cotton wool spot associated with HIV retinopathy are usually superficial, smaller lesions that resolve within few months.<sup>16</sup> Patients with HIV retinopathy rarely have immediate vision loss but there may be damage to the retinal nerve fiber layer, decrease colour vision and also visual field defect.<sup>17</sup> On the other hand, CMV lesions tend to enlarge and coalesce over time to form larger areas of involvement. Some individuals may complain of blurred vision, scotomas, flashlights or floaters. However, approximately 15% of infected patients are often asymptomatic despite the presence of extensive or vision threatening CMV retinitis.<sup>18</sup>

CMV retinitis is the most common cause of blindness in patient with HIV-AIDS. The location of infected retina, determine the risk for vision loss. Posterior retinitis threatens the macula and optic nerve and anterior retina increases the risk of retinal detachment.<sup>15</sup> In this case, the infected retina was posteriorly, which include macula and optic nerve. Hence, the risk of vision threatening was greater. The patient also developed permanent and irreversible visual impairment. Laboratory tests showed a severe decline of CD4+ cell count to only 3 cells/ $\mu$ L. CD4+ cell count of less than 50 cells/ $\mu$ L of patient with HIV/AIDS is a major risk factor for having active CMV retinitis infection.<sup>(19,20)</sup> Data from the Longitudinal Study of the Ocular Complications of AIDS (LSOCA) showed that 90% patients with CMV retinitis had a recent CD4+ cell count of <50 cells/ $\mu$ L and 85% was using Anti retroviral Therapy (ART) prior to CMV diagnosis.<sup>21</sup> Conducting routine ophthalmology examinations especially funduscopy on patients presenting for ART initiation with advanced disease is very important.<sup>21,22</sup>

Before HAART, treatment of CMV retinitis was a lifelong treatment with specific anti CMV therapy that likely to relapsing of retinitis after two until three weeks of discontinuation.<sup>23</sup>

In this HAART era, immune function that is improved by HAART make the cessation of all anti-CMV therapy without reactivation of CMV retinitis possible.<sup>24</sup> Despite such reports, anti-CMV chemotherapies are still involved especially ganciclovir, foscarnet and cidofovir.<sup>25,30</sup> In this case, patient was given oral valganciclovir as induction and maintenance therapy. It was the only drug of choice that was available in our center. Historically, the most utilized antiviral agent has been intravenous ganciclovir. In an attempt to make an oral preparation with convenient dosing that has the safety profile, efficacy and bioavailability comparable to ganciclovir, the prodrug was developed.<sup>26</sup> A randomized control trial study in 2002 showed that valganciclovir, the valine ester of ganciclovir, was found to be as effective as intravenous ganciclovir in more convenient way. In this study, the participants were given oral valganciclovir 900 mg twice daily as induction therapy and the remaining received intravenous ganciclovir 5 mg/kg for three weeks.<sup>27</sup> The main adverse effects of both drugs were diarrhea (30%), neutropenia and anemia (20%).<sup>28</sup> This patient also had been admitted to internal medicine ward due to chronic diarrhea and bicytopenia. So that, patient on oral valganciclovir therapy must undergo complete both ophthalmic and systemic evaluations periodically. Depending the medication used, complete blood count, chemistries and intraocular pressure must be checked. Also dilated eye examinations should be performed daily to weekly initially, then 2 weeks after induction therapy. Patients should be undergone CD4 counts and viral load studies. As well. The other reliable treatment for CMV retinitis is intraocular sustained release ganciclovir implants, which have been very effective in treating CMV retinitis but it is not readily available.<sup>29</sup>

In CMV retinitis management, it is often hard to choose the best therapy for the patient considering the side effects. Oral valganciclovir has been a favourite because it doesn't need IV administration and hospitalization. On the other hand, the cost of the drug is very high, longterm therapy needs strictly good compliance and it causes some toxicities that worsen the condition of immunosuppressed patient. In a point that the patient get remarkable decrease of myelosuppression, sometimes we need to postpone therapy. Consequences, the infection might relapse or remain. It should be avoided if hemoglobin is <8 g%, absolute neutrophil count is less than 500 cells/ $\mu$ L, and the platelet count is less than 25,000/ $\mu$ L.<sup>30</sup> In this case, we needed to postpone valganciclovir maintenance therapy due to bicytopenia. Delay of therapy administration bothered the evaluation of medication result. Patient's visual acuity did not improve after 3 weeks maintenance therapy.

Besides, patient got sight-threatening lesions that close to the macula and optic nerve head. The choice of therapy of this condition is injection of 2 mg ganciclovir or 2.4 mg foscarnet. Those medications were not available in our center. On the follow up examination after valganciclovir induction therapy, fundus evaluation showed a remarkable changes. Exudates and hemorrhages were significantly decreased and the optic disc was easier to evaluate. A pale disc with sclerotic vascularities appeared and his visual acuity was no light perception. As optic atrophy had already set in the vision did not improve even though the chorioretinitis patches had resolved.<sup>31</sup>

Visual loss adds to the overwhelming social and economic burden not only for the patient and family itself but also society. We support routine funduscopic examination that has to be included in the standard WHO care package for HIV-infected patients with advanced disease.<sup>32</sup>

## CONCLUSION

Ocular involvement in HIV/AIDS infected patients is very common with broad spectrum of manifestations including non infectious, infectious and neoplasm. CMV retinitis with involvement of posterior pole or owing retinal detachment is the major factor that causes blindness. As CMV retinitis still exists in the HAART era, we need to conduct ophthalmological examinations as part of routine HIV care. Furthermore, standard treatment guidelines for HIV/AIDS patients with CD4+ cell counts < 100 cells/ $\mu$ L should include ophthalmological screening.

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