Case Report

INTRAVITREAL GANCICLOVIR IN THE MANAGEMENT OF HERPES SIMPLEX VIRUS-2 RELATED ACUTE RETINAL NECROSIS : A CASE REPORT

Rafikah Mahadi*[1], Nor'ain binti Mohd Rawi[2], Rona Asnida Nasaruddin[1], Nurfahzura Mohd Jamil [3]

[1]Department of Ophthalmology, Hospital Shah Alam, Persiaran Kayangan, Seksyen 7, 40000 Shah Alam, Selangor, Malaysia.
[2]Department of Ophthalmology, Faculty of Medicine, University Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia.
[3]Department of Ophthalmology, Hospital Sungai Buloh, Jalan hospital, 47000 Sungai Buloh, Selangor Darul Ehsan, Malaysia.

ARTICLE INFO

Corresponding author:
Dr. Rafikah Mahadi

Email address:
ikamahadi84@gmail.com

Received:
Februari 2022
Accepted for publication:
March 2022

Keywords:
acute retinal necrosis (ARN);
necrotizing retinitis;
intravenous acyclovir;
intravitreal ganciclovir

ABSTRACT

Acute retinal necrosis (ARN) is a rare ocular disease, first reported in 1971. It is characterized by acute pan uveitis with rapidly progressive diffuse full thickness necrotizing retinitis and retinal periarteritis. Several treatment regimens have been advocated for ARN, from systemic oral or intravenous, with or without intravitreal antiviral. We report a case of an ARN secondary to HSV-2 infection treated with intravenous acyclovir and intravitreal ganciclovir.

INTRODUCTION

Acute retinal necrosis (ARN) is a rare viral uveitis syndrome manifest as panuveitis with one or more foci of retinal necrosis with discrete borders, located in the peripheral retina and retinal periarteritis which rapidly progress [1]. It occurs as a result of reactivation of latent viral infection. The etiologies of ARN include various members of the herpes family such as varicella zoster virus (VZV), herpes simplex 1 and 2 (HSV-1, HSV-2), cytomegalovirus (CMV), and infrequently, Epstein-Barr virus (EBV). In elderly, the incidence of HSV-zz1 and VZV is more frequent, meanwhile in younger patients, HSV-2 is more common [2].

ARN may potentially lead to severe visual loss from devastating complications of retinal detachment if left untreated. Meanwhile, in some studies, visual prognosis is guarded even with treatment [3]. The aim of treatment includes immediate control of both viral multiplication and inflammation. Several treatments regimens have been advocated since there are reported successful outcomes with intravenous acyclovir alone or intravitreal injection of antiviral with and without concurrent systemic antiviral and corticosteroids [1]. Treatment with intravitreal injection of ganciclovir in ARN patients on systemic intravenous antiviral medication has been reported satisfactorily in few studies [4]. In this case report, we describe an ARN case whom was on intravenous acyclovir with the addition of intravitreal injection of ganciclovir in controlling the viral load and reducing the ocular inflammation.

CASE PRESENTATION

A 17-year-old male patient presented with unilateral left panuveitis, dense vitritis and peripheral multifocal retinitis (Figure 1). He had a history of childhood chicken pox infection. His main complaint was blurring of left vision, progressively worsening for one week prior to presentation. He has left periorbital discomfort and photophobia. Otherwise, there were no floaters or flashes.

At the initial examination, his left best corrected visual acuity (BCVA) was only 1/60. No associated ocular involvement such as typical rash as in herpes zoster ophthalmicus (HZO) observed. Left anterior segment examination revealed granulomatous keratic precipitates, cells of 2+,intraocular pressure (IOP) of 17 mm Hg. Otherwise, there were no posterior synechiae, peripheral anterior synechiae of iris atrophy or iris nodule. Posterior segment

revealed dense vitritis with swollen disc. There was multifocal full thickness peripheral necrotizing retinitis associated with haemorrhages and arteriolar sheathing.

The right eye was exotropic with a vision of counting fingers without evidence of active inflammation. Patient had a history of red eye during childhood however parents did not seek any treatment and his vision subsequently became poor. There was evidence of previous ocular inflammation with posterior synechiae and cataractous lens. Otherwise, no anterior chamber cells keratic precipitates, iris nodules or iris atrophy. Fundus view was hazy and B scan revealed retinal detachment.

Left acute retinal necrosis was diagnosed. Left aqueous tap was done and aqueous fluid was sent for viral polymerase chain reaction (PCR) for HSV/ VZV/CMV. Patient was also screened for systemic infectious disease such as human immunodeficiency virus (HIV), Hepatitis B and C. The results were however non-reactive. The patient was then started on intravenous (IV) Acyclovir 660 mg TDS (based on his body weight) for 14 days with renal function monitoring.

After 48 hours of IV Acyclovir, anti-inflammatory dose oral prednisolone 0.5 mg per kg body weight daily was started. Polymerase chain reaction (PCR) from his aqueous sample came back as positive for HSV-2. In view of deterioration of his renal function and slow ocular improvement, he was then counseled for intravitreal ganciclovir 2 mg/0.1 ml injection.

Three days post intravitreal injection, his left BCVA improved to 6/20 with evidence of improving vitritis, retinitis and reduced haemorrhages (Figure 2). His kidney function slowly improved as well. He subsequently underwent second intravitreal ganciclovir 2 mg/0.1 ml injection (Figure 3).

On treatment day 12, he developed inferior retinal detachment secondary to confluent retinal breaks inferotemporally (Figure 4). However, his left visual acuity was maintained at 6/30 with pinhole 6/20. The anterior chamber still showed moderate inflammation although most of the keratic

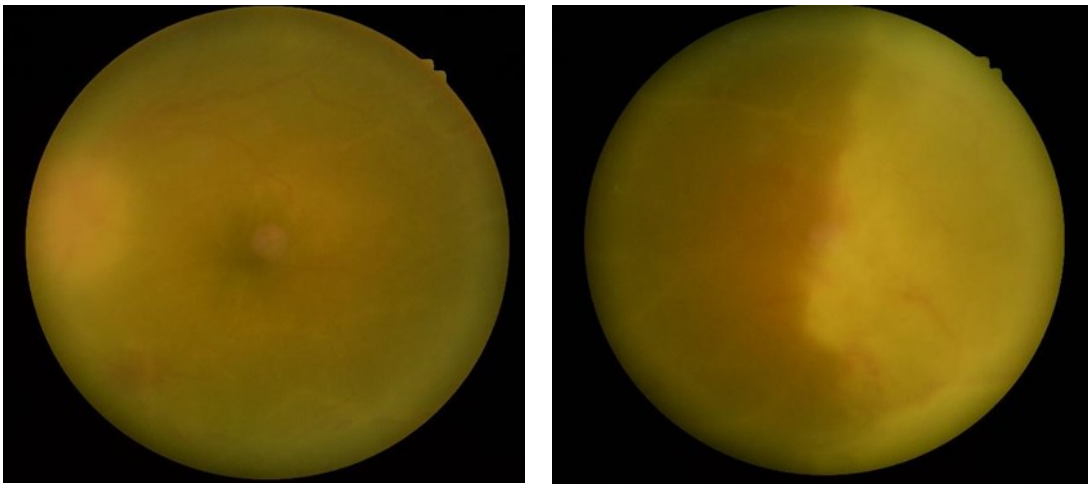

Figure 1: Left fundus showing hazy media due to severe vitritis, with peripheral retinal necrosis haemorrhages and swollen optic disc

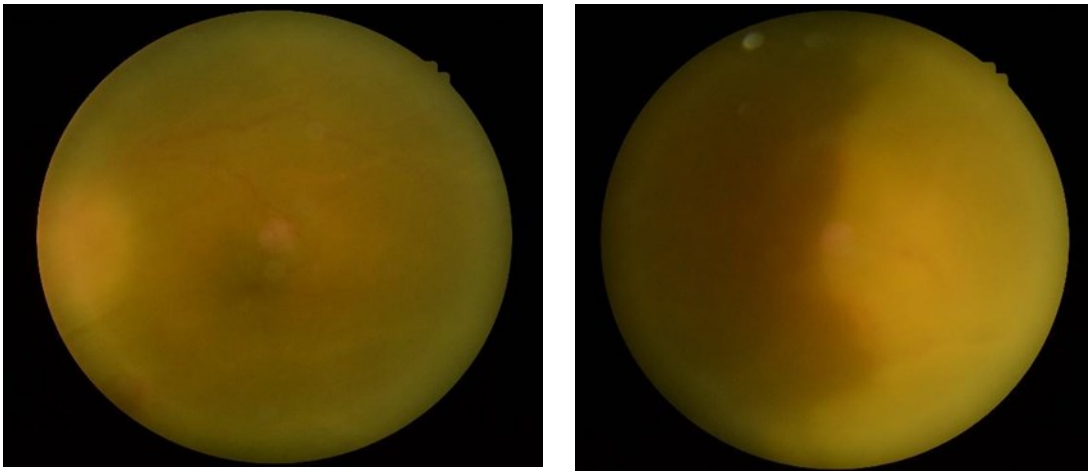

Figure 2: Left fundus showing improving vitritis, peripheral retinal necrosis, lesser retinal haemorrhages

precipitates had resolved. The location of the KP was mostly inferior. The patient then underwent left vitrectomy with endolaser and silicone oil tamponade.

DISCUSSION

The incidence of ARN is rare worldwide and even in Malaysia. However, due to its potential visual debilitating complications caused by ARN it warrants early clinical recognition and prompt treatment initiation to avoid serious ocular sequelae.

Based on diagnostic criteria proposed by the American Uveitis Society in 1994, ARN consists of single or multiple areas of distinct retinal necrosis, with rapid progression without antiherpetic treatment, and characteristic of extension of necrosis in circumferential pattern, presence of occlusive vasculopathy especially arteriolar involvement, and presence of anterior chamber and vitreous inflammation [5].

Etiology of disease is due to reactivation of latent herpetic viral infection and herpes simplex virus (HSV) with varicella zoster virus (VZV) being the most common cause. Other members of the herpes virus family which is less often associated with ARN include cytomegalovirus (CMV) and Epstein-Barr virus (EBV) [2].

Although ARN can affect young and healthy individuals, nowadays it does affect both the immunocompetent and immunocompromised population. The immune status of the patient determines the clinical course and outcome of the disease. Thus, it is important to exclude preexisting immunocompromised states such as HIV infection.

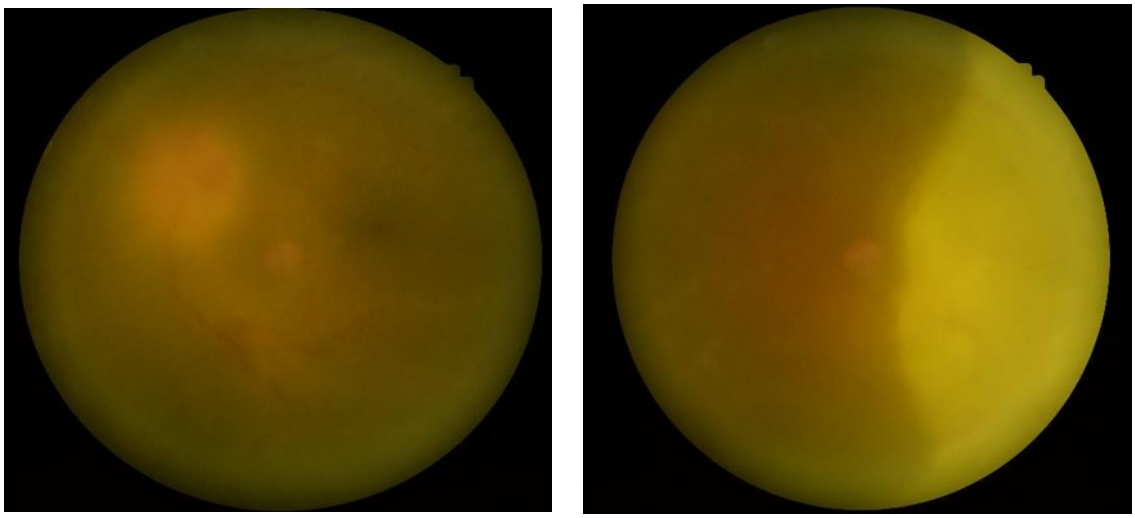

Figure 3: Left fundus after second intravitreal Ganciclovir

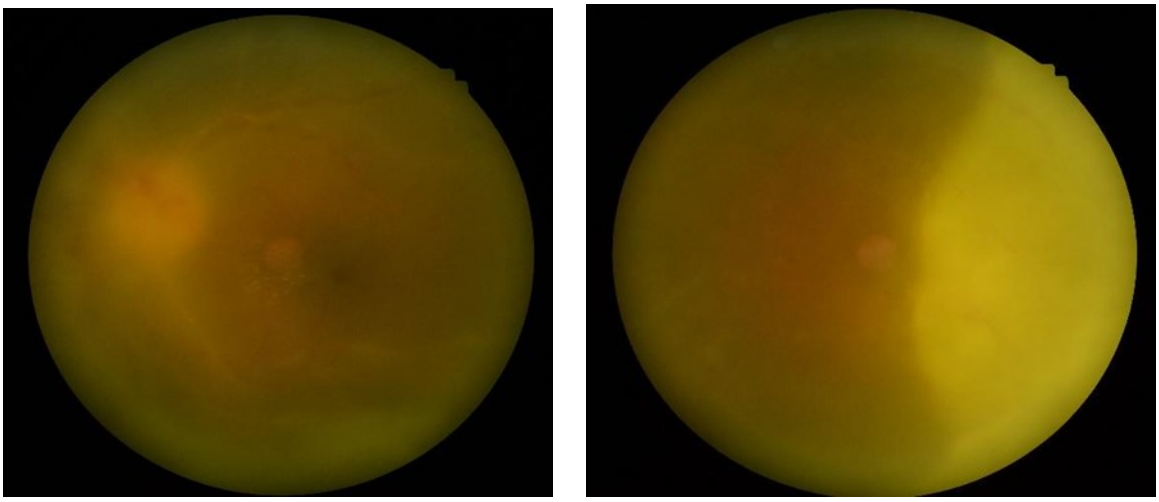

Figure 4: Left fundus after 12 days of treatment

The goal of ARN treatment includes reducing ocular viral load, halting the retinal necrosis area in order to avoid devastating complications such as retinal break which lead to sight threatening retinal detachment. Another goal is to minimize the severe inflammation and to prevent further collateral damage such as vascular occlusions besides protecting the fellow eye involvement. The systemic antiviral treatment commencement either orally or intravenously should not be delayed till laboratory results are ready.

Acyclovir and its prodrug valacyclovir are both potent viral DNA polymerase inhibitors and have been shown very effective in treating VZV and HSV viral infection. Acyclovir is a deoxyguanosine analogue with an acyclic side chain which lacks of 3′-hydoxyl group of natural nucleosides. It is preferentially attracted to the infected cells. Acyclovir is then monophosphorylated by virus-encoded thymidine kinase. Host cell thymidine kinase is less capable of converting acyclovir to its monophosphate derivative. Subsequently diphosphorylation and triphosphorylation are catalyzed by host cell enzymes, resulting in acyclovir triphosphate concentrations which are 40 to 100 times higher in HSV-infected cells than in uninfected cells. Acyclovir triphosphate thus prevents viral DNA synthesis by inhibiting the viral DNA polymerase [6,7].

In a study by Palay et al, the use of intravenous acyclovir in comparison to observational case series showed that the contralateral eyes of 87% of treated eyes remained quiet compared to 30% of the untreated patients [8]. Systemic monitoring is warranted once a patient is started with acyclovir. Side effects of acyclovir include neurotoxicity and nephrotoxicity due to a crystalline nephropathy. Other side effects include headache, rash, and gastrointestinal symptoms [6].

Valacyclovir is the L-valyl ester of acyclovir in which it is rapidly converted to acyclovir after oral administration by first-pass metabolism in the liver. Thus, it has higher bioavailability than intravenous acyclovir. Huynh et al reported that oral valacyclovir can reach a concentrations in the vitreous and achieve inhibitory ranges of HSV-1, HSV -2 and VZV [9]. However, valacyclovir commencement in particularly immunocompromised patients should be used judiciously as this group has higher risk for nephrotoxicity and thrombocytopenia – specifically for thrombotic thrombocytopenic purpura or hemolytic uremic syndrome (TTP/HUS) [7].

Intravitreal antiviral treatments have been advocated as an adjunct to the systemic ARN treatment [10]. Intravitreal Foscarnet or ganciclovir injection have been reported in some studies and it is administered either as a one-time treatment or as induction followed by maintenance treatments. Ophthalmologists may consider the intravitreal antiviral as an adjunct if the disease fails to respond to the standard of care treatment as the ARN can be caused by different members of the herpes virus family. There are also cases of patients with systemic treatments who do not tolerate the systemic antiviral drug and thus intravitreal antiviral injection may offer higher therapeutic levels, which cannot be achieved by systemic antiviral. This is due to the human blood ocular barrier [11].

Foscarnet (trisodium phosphonoformate) is a pyrophosphate analog. The mechanism of action is it binds reversibly near the pyrophosphate-binding site of DNA polymerase (or reverse transcriptase) without requiring further modification [12]. After binding, the drug inhibits the cleavage of the pyrophosphate moiety from deoxynucleotide triphosphates, and halts DNA chain elongation. However, it has low bioavailability and is only available for intravenous and intravitreal usage.

Ganciclovir is a nucleoside analogue that differs from acyclovir as it has an extra hydroxymethyl group on the acyclic side chain. Ganciclovir is then phosphorylated by a virus-encoded enzyme, and further by cellular enzymes. Ganciclovir triphosphate is a competitive inhibitor of herpes viral DNA polymerases, which will terminate the DNA chain elongation. Ganciclovir triphosphate also inhibits activity against cellular DNA polymerases. Ganciclovir has some similar activity to acyclovir particularly against HSV-1, HSV-2, and VZV however, on contrary of acyclovir, it has greatest activity against CMV.

Meghpara et al reported that patients with moderate disease (25–50% retinal involvement) had favorable response with intravitreal injection of ganciclovir or foscarnet in ARN patient [4]. Kauffman et al reported the similar efficacy and result for both intravitreal ganciclovir or foscarnet. Both intravitreal antivirals had demonstrated significant and early resolution of ARN in the report. The report also suggested that intravitreal antivirals could be reserved for those patients who cannot tolerate the systemic side effects of antivirals [11]. Patel et al study on 8 years' case series of ARN revealed 29% of eyes had final BCVA better than 20/200 with intravitreal ganciclovir or foscarnet despite being on systemic antiviral [13]. Lee et al reported that IVT foscarnet was efficacious in ARN and can be used as the only treatment in patients with intolerance to systemic antivirals [14]. While Chau Tran et al case series of HSV-2 ARN showed that 41.7% patients had visual improvement of two or more lines with intravenous acyclovir or foscarnet +/- intravitreal ganciclovir +/- interferon [15].

Acute retinal necrosis can cause severe inflammatory response and may manifest as moderate to severe vitritis with significant retinal necrosis. The role of systemic corticosteroids is to decrease ocular inflammation in a controlled ocular viral load situation [12]. As in our case, it is usually started after 48 hours of antiviral treatment. The ocular inflammation may lead to occlusive vasculitis and/or arteritis secondary to infiltration of inflammatory cells. Although anticoagulants and aspirin have been advocated in some studies, its administration is less commonly used.

Prognosis for visual recovery is guarded with treatment and tends to be very poor without treatment. Complications are retinal holes and tears, retinal detachment, proliferative vitreoretinopathy, vitreous haemorrhage, epiretinal membrane and optic neuropathy.

CONCLUSION

Several treatment regimens have been advocated in many studies. However due to its rare incidence, the standard of care treatment is still based on the reported successful cases with systemic intravenous acyclovir. We report this case due to the rarity of the ARN incidence and few studies that report regarding the standard treatment of ARN either with systemic antiviral orally or intravenously with adjunct intravitreal antiviral. Further studies are needed to determine the potential efficacy of different types of antiviral in ARN patients. Meanwhile, few studies suggested intravitreal dexamethasone used in conjunction with intravitreal antiviral agents in the management of ARN. This might be useful in order to reduce the ocular viral load as well as to control the ocular inflammation that occurs concurrently [12].

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