

TREATMENT OF CYTOMEGALOVIRUS RETINITIS WITH INTRAVITREAL GANCICLOVIR: A Case Report

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SUMMARY

A 60-year-old male on chemotherapy for multiple myeloma developed cytomegalovirus (CMV) retinitis in one eye. He was commenced on intravenous ganciclovir. This regime had to be modified, however, in view of the fact that he had bone marrow neoplasia (multiple myeloma) and was on chemotherapy. Since intravenous ganciclovir causes bone marrow aplasia, this could worsen his clinical state rapidly. He therefore had a ganciclovir implant inserted into his vitreous. This was to prevent the systemic effects of ganciclovir on the bone marrow.

This paper highlights the possibility of CMV retinitis in immunocompromised non-AIDS adults, the clinical manifestation of CMV retinitis in non-AIDS immunocompromised patients, and the relative advantage of intravitreal sustained release ganciclovir implants over systemic treatment in selected patients.

Key words: cytomegalovirus retinitis, ganciclovir implant, non-AIDS retinitis

INTRODUCTION

Cytomegalovirus retinitis has long been recognized as an opportunistic infection in immunocompromised individuals, such as those with lymphoreticular malignancy and those on chemotherapy.¹

In more recent times, it has been reported often among patients with the acquired immunodeficiency syndrome (AIDS).² There is a high prevalence of anti-CMV antibodies in the general population.³ In most individuals, CMV remains latent, but in those who are immunocompromised, reactivation may occur. In rare cases, immunocompromised individuals experience their first exposure to CMV and contract the infection.

There have been few reports on CMV and CMV retinitis in the Nigerian and African literature. This is because until recently in Nigeria, it was not easy to obtain drugs for the treatment of AIDS. Most of the patients died of other complications before CMV infection could occur.^{4,5} In South Africa, no cases presented before 1996, when highly active anti-retroviral therapy (HAART) became available there.⁴

Now that the Nigerian government has begun to maximally subsidize the cost of anti-retroviral drugs, we are likely to have higher survival rates, and therefore, more cases of CMV retinitis and other retinitis of opportunistic origin may begin to present than previously reported.

Systemic anti-CMV drugs are very expensive, have many side effects, and are generally not as effective as local treatment.⁴ Two methods of using intravitreal ganciclovir have been reported.^{2,4} One method is to use repeated doses of intravitreal ganciclovir, initially twice weekly for induction and then weekly for 6 or more weeks.⁴

The other method is to use a ganciclovir implant intravitreally.² The effect of this in the eye lasts for 6-8 months.

This paper shows that people with severe immunodeficiency due to non-AIDS diseases can present with CMV retinitis, which is highly comparable or similar to that already described in the literature on AIDS cases. It also highlights the clinical manifestation of non-AIDS CMV retinitis, and the value of intravitreal ganciclovir implants when a patient cannot be treated systemically.

CASE REPORT

A 60-year old African-American male presented to the Eye Clinic of the University of Maryland, Baltimore, United States of America (USA) on November 23, 1997 with progressive blurring of vision in the right eye of 8

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months duration. He had been diagnosed with multiple myeloma in February 1997 and started on chemotherapy, which he received monthly. Other medications included ciprofloxacin, acyclovir, diflucan and augmentin. While on chemotherapy, he reported crusting of the lids in both eyes and worsening vision. The oncologist therefore suspended this treatment in November and advised him to seek ophthalmic attention.

On presentation at the clinic, his best corrected visual acuity was OD 20/200 and OS 20/30. Intraocular pressures were 32 mmHg and 20 mmHg respectively. The right eye had 1+ conjunctival injection, 2+ microcystic corneal oedema, 3+ mutton fat keratic precipitates and 3+ vitreous inflammation. A white retinal lesion with retinal haemorrhage and sheathing of retinal vessels was faintly detectable inferior to the disc, between the arcades at 5 and 6 o'clock. The left eye was normal.

The clinical characteristics were suggestive of CMV retinitis, although toxoplasmosis and herpes zoster retinitis were also considered. Serology was positive for CMV IgG. The patient was commenced on an induction dose of intravenous ganciclovir 5mg/kg every 12 hours for 14 days (ganciclovir is 9, 2 hydroxypropoxymethyl guanine). Timolol maleate 0.5%, cyclopentolate 1% and prednisolone acetate 1% were also prescribed.

Two weeks later, visual acuity was 20/100 in the right eye, anterior segment and vitreous inflammation had improved, while the white retinal lesion remained the same size. In a discussion with the oncologist, it was considered necessary to have a more localized treatment since the patient had bone marrow neoplasia. A ganciclovir implant was therefore inserted inferotemporally, through the pars plana, into the vitreous on December 17, 1997, in order to minimize bone marrow and other systemic toxicity associated with intravenous ganciclovir.

The patient's vision worsened temporarily to 20/300 a day after surgery because of mild vitreous haemorrhage, but within two weeks it had improved to 20/60. He was recommenced on chemotherapy by the oncologist and had successful bone marrow transplantation in January 1998, without a flare-up of ocular inflammation. Three months after the ganciclovir implantation, visual acuity in the right eye was 20/40 with no vitreous inflammation and quiescent retinitis, which appeared as an area of retinal atrophy and retinal pigment epithelium disturbance, inferior to the disc.

SURGICAL METHOD

Maximum pupillary dilatation was obtained by the application of 5% homatropine and 10% phenylephrine drops every 10 minutes for a total of 5-6 applications, beginning 90 minutes before the operation.

Surgery was carried out using local anaesthesia

consisting of 4% lidocaine mixed in equal parts with 0.75% bupivacaine. Facial block and retrobulbar injections were given. A lateral canthotomy was also done after infiltrating the region with a local anaesthetic.

The patient was draped, and using an operating microscope, the inferior conjunctiva was reflected and episcleral vessels were cauterized. Two partial thickness sclera flaps, 3mm x 1.5mm, were raised at the pars plana (4mm posterior to the anterior margin of the limbus). A standard 20 gauge, size 3mm width ALCON disposable blade was introduced radially to make two 3mm sclerotomies in the pars plana, at the 7 o'clock and 4 o'clock positions. The vitreal manoeuvres were illuminated by the fibre optic probe with microscope light off, but leaving the focusing and zoom functions operational. The fibre optic probe was inserted at 4 o'clock while the ganciclovir plaque (VITRASERT) was gently inserted into the vitreous with a 0.12 forceps through the 7 o'clock sclerotomy and anchored to one lip of the sclerotomy by its suture (manufactured with a suture attached). The scleral and conjunctival flaps were then replaced with 9/0 nylon.

A subconjunctival antibiotic (gentamycin 20mg) and a steroid (betamethasone 4mg) were administered with topical cyclopentolate 1% at the end of surgery.

The second author was the surgeon while the first author assisted.

DISCUSSION

The diagnosis of retinitis in immunocompromised patients may be difficult because the clinical appearance of various causes of infectious retinitis may overlap.^{6,8} Among the most common causes of infectious retinitis in immunocompromised individuals are: viral infections such as CMV, herpes simplex (HSV) and herpes zoster (HZV); parasitic infections such as toxoplasmosis and bacterial infections such as syphilis.

In AIDS patients, CMV retinitis usually causes minimal intraocular inflammation, while in non-AIDS patients on chemotherapy, a more severe inflammatory reaction may occur.^{6,8} Toxoplasmosis presents with more vitreous haze than the other causes of retinitis (the so-called 'headlight in the fog' appearance), and so can be confused with severe CMV retinitis in non-AIDS immunocompromised patients.⁹ Unfortunately, positive serology is not very helpful in distinguishing between these diseases because there is a high prevalence of serum antibodies of both in the adult population.² A negative serology is more informative however, and helps to exclude the disease from the differential diagnosis.⁷ The clinical appearance of the retinal lesion often helps to determine the diagnosis. CMV retinitis often presents as a white, well demarcated geographical area of retinal necrosis associated with retinal haemorrhages and retinal venous sheathing. It is slowly progressive and if untreated, results in widespread

retinal destruction.⁷⁻¹⁰ Our patient's retinal lesion was comparable to the features described above for CMV retinitis in non-AIDS patients.

CMV retinitis has been reported to be the most frequent cause of retinitis in severely immunocompromised patients, especially once the CD4 helper T cell count is below 50/mm.³ Herpes simplex accounts for 40% and syphilis for 1% of these.¹¹⁻¹² Although HSV, HZV, CMV and syphilis may also cause an acute deep retinal necrosis, which is often a more rapidly devastating inflammation than what we saw in our patient, HSV, HZV and syphilis usually present as multifocal choroiditis, while toxoplasmosis often presents with satellite lesions around an old lesion.⁷⁻¹³ Specific antibody laboratory tests such as FTA Abs (fluorescent treponemal antibody) test and VDRL are very helpful in the diagnosis of syphilis.

Intravenous ganciclovir, foscarnet, cidofovir, and recently fomivirsen, have been reported to be very effective for CMV retinitis, the only drawback is that patients (AIDS patients) with CMV retinitis have to use them for life. These are administered through indwelling intravenous catheters, which predispose them to infections. Of course, this completely changes the life-style of the patient.¹¹⁻¹⁴ They are, however, not as effective as local treatment.^{2,4,15,16}

In addition, ganciclovir causes bone marrow suppression, while foscarnet causes renal toxicity and severe electrolyte imbalance.³ Intravitreal ganciclovir implants have been found to be useful in providing a higher concentration of the drug in the eye, where it is needed. Preliminary studies on intravitreal ganciclovir have proved encouraging, as newly diagnosed cases of CMV retinitis quieten within two weeks.¹⁵⁻¹⁶ Possible complications of the procedure include endophthalmitis, vitreous haemorrhage and retinal detachment. Since our patient did not have a systemic disease and also needed a bone marrow-sparing medication (both multiple myeloma and chemotherapy compromised his bone marrow function), the intravitreal slow-release ganciclovir implant was obviously a better alternative.

Intravitreal injections of ganciclovir and cidofovir are also available. But these will need to be repeated weekly over 4-6 weeks to prevent a relapse.⁴ These frequently repeated injections, though cheaper than an implant, have the risk of repeated vitreous haemorrhage, cataract, hyphaema, retinal detachment and endophthalmitis.⁴

The intravitreal drug could be combined with an intravenous one in another setting.⁴ Our patient showed prompt improvement with the implant, proving that the concentration reaching the retina was adequate. It does not have systemic absorption, and therefore avoids systemic effects and drug interactions.^{2,15,16} The implant which is usually effective for 6-8 months is a 4.5 milligram preparation, with a rate of release of one

microgram per hour.² In AIDS patients, if the CD4 count remains low, the median time for retinitis progression is 216 days in ganciclovir implant patients versus 104 days for those on intravenous drugs.¹⁶ The sustained release ganciclovir implant appears to be highly effective for the treatment of CMV retinitis and at a lower cost. While treatment with foscarnet is estimated at \$50,000 per year, a slow release implant costs \$5,000 per implant.^{2,15}

It is hoped that large pharmaceutical companies will work towards producing a cheaper ganciclovir implant for the developing world.

CONCLUSION AND RECOMMENDATION

The availability of ganciclovir is a medical intervention in the natural history of ocular CMV. Its use, however, is intravenous and may be needed throughout life. This is cumbersome, with attendant risk of systemic complications. The risk of developing bone marrow and kidney complications is greatly reduced with intravitreal ganciclovir. It is also cost effective.

Since intravitreal ganciclovir injections may need to be repeated up to 8 times for each patient and at weekly intervals; the risk of ocular damage is heightened.

A single insert of intravitreal implant of ganciclovir will last 6-8 months. The production of a cheaper implant for the developing world will be needed as the survival rate of HIV infection increases in Africa.

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