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Case report

Rapid regression of cystoid macular edema associated with cytomegalovirus retinitis in adult acute myeloid leukemia by intravitreal methotrexate combined with oral valganciclovir: A case report with comparison of binocular outcome

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ABSTRACT

Cytomegalovirus (CMV) retinitis is a late complication of organ and hematopoietic stem cell transplant, the risk of which depends on the degree of immunosuppression. With the institution of preemptive ganciclovir therapy early after transplant, most patients survive episodes of life-threatening CMV infection during the early months (usually the first 3 months) after transplant and hence late onset of CMV disease, such as CMV retinitis, is being recognized more frequently. Direct involvement of the macula or optic head remains the leading cause of visual loss in patients with CMV retinitis, but there are few studies investigating the management of this condition.

Herein, we present the case of 28-year-old man who had acute myeloid leukemia and developed CMV retinitis with bilateral cystoid macular edema and optic swelling in the right eye 6 months after bone marrow transplant. He received treatment with intravitreal methotrexate in the right eye in combination with oral valganciclovir. Visual acuity improved 1 month after four weekly injections of intravitreal methotrexate 400 μg/0.1 mL. Resolved disc swelling and regression of macular edema were also observed. By comparing binocular outcome, we present our findings and discuss the possible efficacy and safety of this treatment with respect to regression of anatomical damage and improvement in visual acuity.

1. Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus belonging to the human herpesvirus family, which includes herpes simplex virus, varicella zoster virus, and Epstein–Barr virus. Clinical characteristics of systemic CMV infections were initially described in 1905.[1]

Human immunodeficiency virus (HIV) infection is the most common cause of immunosuppression leading to reactivation of CMV and symptomatic infection. Severe CMV infection has also been associated with congenital immunodeficiency syndromes, pharmacologic immunosuppression, organ transplantation, malignancy, and autoimmune disorders.[2] CMV infection is the leading viral cause of morbidity and mortality in patients receiving hematopoietic stem cell transplants (HSCTs) or solid organ transplants (SOTs).[3]

One of the major targets of CMV infection is the retina.[4] Although the virus was long known as a human pathogen, CMV infection of the retina was not described until the 1950s.[5] CMV was proven to be the causative agent in presumed CMV retinitis in 1964.[6] CMV retinitis was the AIDS-defining diagnosis in about 5% of

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patients with HIV infections.[7] Among SOT patients, <2% develop CMV retinitis; however, the pediatric population is at a higher risk.[8] After HSCT, the only large study published on CMV retinitis development showed an incidence of 1.4% in patients who were alive 100 days post-transplant.[9]

CMV retinitis is bilateral in approximately one third of patients.[10] It is a relentless, slowly progressive infection, which, if not treated, may result in blindness caused by total retinal necrosis, retinal detachment, optic nerve involvement, or a combination of several of these factors. Immune-mediated vascular damage may also play a role in vasculitis.

Immediate, acute loss of central vision early in the disease course rarely occurs.[11] The causes of severe central visual loss include CMV infection of the macular or optic nerve, macular serous exudation, and cystoid macular edema (CME). CMV can either infect the optic nerve directly or by extension from adjacent retinitis.[12] In the former case, optic neuritis with profound, irreversible visual loss usually develops. With CMV infection involving the disc or macular retina, an exudative neurosensory detachment develops around the optic nerve, macula, or both, often with the formation of a macular star of consisting of lipid exudation.[13]

Previous results showed that ganciclovir alone (systemic or intraocular administration) is less effective for CME in CMV retinitis probably because of the inflammatory processes associated with CME. CME tends to develop late in the clinical course, such as in the setting of resolving CMV retinitis in non-HIV patients[14] and in the case of immune-reconstitution syndrome in HIV patients.[15] Anti-inflammatory or immunomodulatory agents, in addition to ganciclovir, may be considered in such situations.

The present case is of a patient with adult acute myeloid leukemia who developed CMV retinitis with bilateral CME and associated subretinal fluid 6 months after HSCT. Optic swelling was also observed in the right eye. Hesitant to receive intravitreal ganciclovir injections twice a week in both eyes, he accepted treatment with less frequent intravitreal injection of methotrexate (MTX) once a week in his right eye (which had more severe symptoms) in combination with oral valganciclovir. With comparison of binocular outcome, we present our findings and discuss the possible efficacy and safety of this therapy for regression of macular damage and improvement in visual acuity.

2. Case Report

A 28-year-old man had acute myeloid leukemia, M2 (Chr: 46,XY {6}; MLL-PTD[−], NPM1[−], FLT3-ITD[−]) and completed chemotherapy in June 2012. He had a relapse 1 year later and received reinduction chemotherapy in June 2013 and bone marrow transplant in November, 2013. CMV disease with gastrointestinal manifestation was diagnosed 7 weeks later by the detection of CMV DNA in plasma samples using real-time polymerase chain reaction (PCR). The patient received antiviral treatment with intravenous (IV) ganciclovir 450 mg (5 mg/kg) twice daily for 2 weeks until two consecutive samples of plasma negative for CMV PCR were obtained.

In May 2014, he was referred to our clinic as he had been experiencing deteriorating vision in both eyes for 2 weeks. At the first visit, his best corrected visual acuity was counting fingers at 20 cm (2 logMAR units) in his right eye (OD) and 20/100 (0.3 logMAR units) in his left eye (OS).

Slit-lamp biomicroscopic examination of the anterior chamber in OS yielded normal results, whereas a 1+ anterior chamber cellular reaction was observed in OD. On indirect ophthalmoscopy, changes typical of CMV retinitis were observed, such as areas of yellow–white necrosis with vascular sheathing along the distribution of retinal vessels of the superior arc in OS and both the superior and inferior arcs in OD. Exudates and edema were also noted with varying degrees of hemorrhage, which presented with a brushfire pattern. Optic disc swelling was also noted in OD, which had worse visual acuity. Vitreous inflammation was mild in both eyes (Figure 1).

Optical coherence tomography showed CME with subretinal fluid in both eyes (Figure 2). Central macular thickness was 508 μm OD and 567 μm OS. On laboratory examination, CMV was identified in the aqueous humor of both eyes using PCR. The patient's hemograms revealed a relative immunocompetent status 1 month before and after he visited our clinic; however, PCR results for plasma CMV infection were positive again at that time.

CMV retinitis with right optic neuritis and bilateral macular edema was diagnosed. Since the patient was hesitant to accept frequent intravitreal injections of ganciclovir, it was decided to administer oral valganciclovir with an induction dose of 900 mg twice a day for 3 weeks and a weekly adjuvant intravitreal injection of MTX 400 μg/0.1 mL unilateral in OD, the more severely affected eye, for 1 month.

Best corrected visual acuity improved to 20/400 (1.3 logMAR units) after four MTX injections and to 20/63 (0.5 logMAR units) OS a month later. Indirect ophthalmoscopy revealed resolving disc swelling in OD (Figure 3) and follow-up optical coherence tomography revealed that macular edema had subsided in MTX-injected eyes, but persisted OS (Figure 4). A maintenance dose of valganciclovir 900 mg orally once a day was continued. No recurrence of

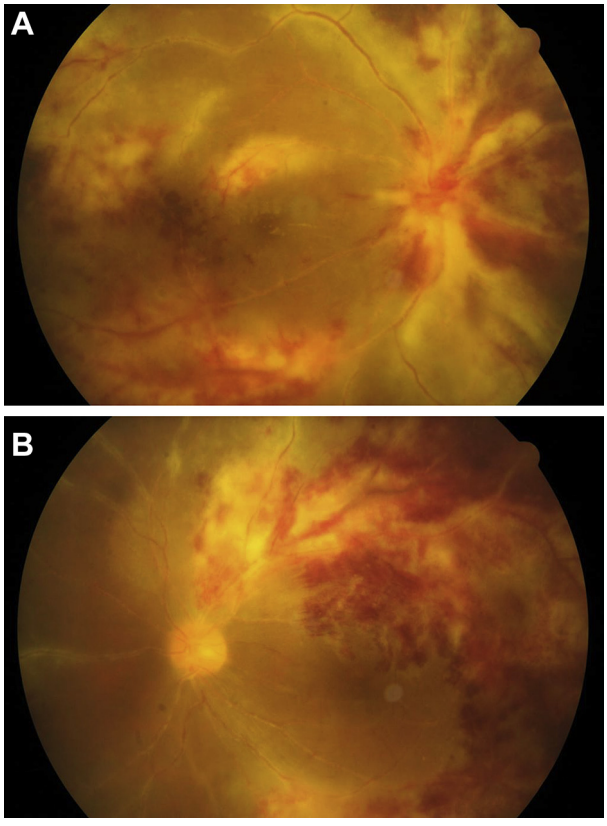

Figure 1. Classic changes of cytomegalovirus retinitis appeared as areas of yellow-white necrosis with vascular sheathing along the distribution of retinal vessel of (B) the superior arc in the left eye and (A) both superior and inferior arcs in the right eye. Exudates and edema were also noted with variable amounts of associated brushfire pattern hemorrhage. Vitreous inflammation was mild and zone 1 involvement was showed in both eyes. Optic disc swelling was also noted in the right eye, which had worse visual acuity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

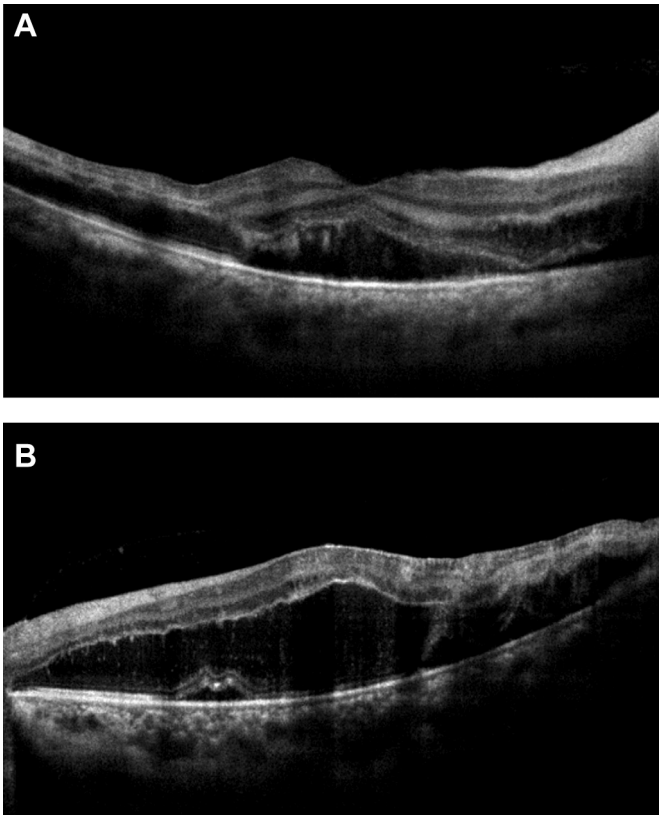

Figure 2. The optical coherence tomography showed cystoid macular edema with subretinal fluid in (A) the right eye and (B) the left eye.

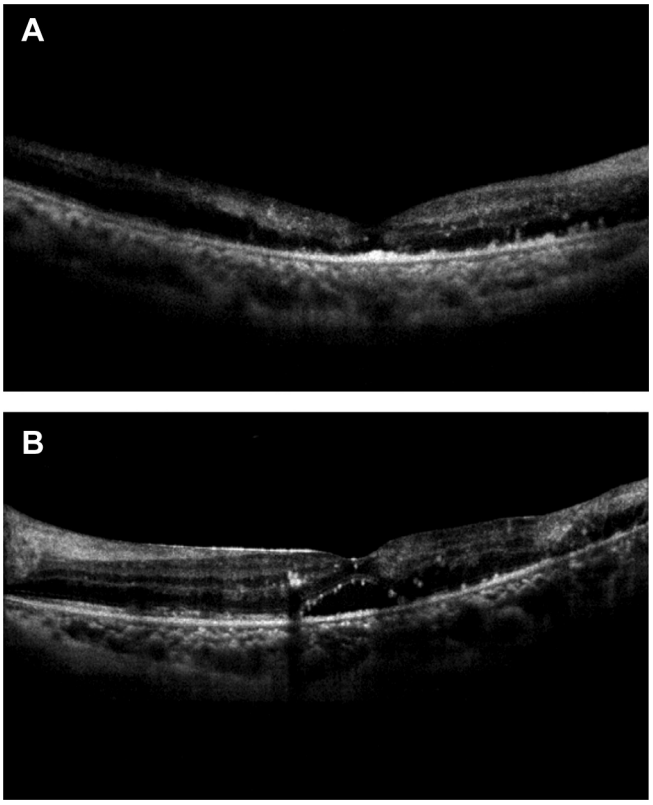

Figure 4. Four weeks after treatment, the optical coherence tomography follow-up showed that macular edema (A) subsided in intravitreal methotrexate-injected eyes but (B) persisted in the left eye.

macular edema OD and no ocular side effects were observed during the next 8 months of follow up.

3. Discussion

In immunosuppressed patients, retinitis can result from hematological dissemination of reactivated CMV as well as from exogenously acquired CMV. Although CMV retinitis is the most common clinical complication of CMV reactivation in HIV-infected patients, it is only infrequently reported in HSCT recipients. However, preemptive ganciclovir therapy early after transplant[16] allows most HSCT recipients to survive life-threatening CMV infection during the early months (usually the first 3 months) after transplant, and hence late onset of CMV disease is being recognized more frequently.

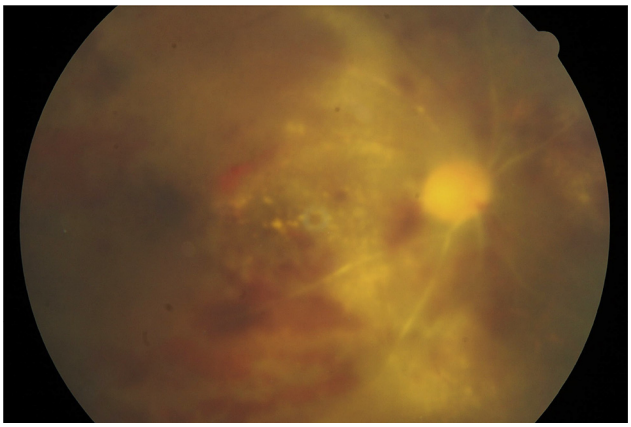

Figure 3. The color fundus picture showed resolving disc swelling in the right eye 4 weeks after treatment. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In a study by Crippa et al,[8] CMV retinitis was found to be a late complication of HSCT and was mainly seen in patients with antecedent CMV reactivation or disease. The median time of diagnosis of CMV retinitis was 251 days (range, 106–356 days). Similarly, our patient presented with CMV viremia with gastrointestinal manifestation within 7 weeks of HSCT, and developed visual symptoms 6 months after HSCT.

At onset, CMV retinitis may show only a few symptoms, providing scant evidence of the infection's potential to cause severe visual loss.[9] The presence of symptoms is often related to the retinal location involved. CMV retinitis affecting the posterior pole is more often symptomatic than peripherally located retinitis. Silverstein et al[13] reported prominent loss of vision associated with CME in seven eyes with CMV retinitis in AIDS patients. In each patient, the area of retinitis involved zone 1. Our patient also showed zone 1 involvement in both eyes, which was indicative of the development of worse macular complications. Furthermore, CMV papillitis, a very unusual complication of CMV infection causing disc swelling and less reversible visual loss, has even been reported in an immunocompetent patient. In our patient, optic disc swelling resolved after 1 month of therapy, but with sequelae of occluded retinal vessels. Immune-mediated vascular damage may play a role in papillitis. As in our case, this patient too did not seek medical treatment until severe vision loss caused by macular and papillary involvement occurred.

Ganciclovir is an acyclovir analog and was the first antiviral agent to be approved for the treatment of CMV disease; it remains

the first-line treatment for CMV infection and CMV disease in transplant recipients.[17] The incidence of CMV disease occurring within the first 100 days post-transplant was significantly less with ganciclovir compared to placebo[18] and patients receiving ganciclovir had significantly greater overall survival than the placebo group at both 100 days and 180 days post-transplant.[19]

IV ganciclovir (Cytovene-IV, Roche, Basel Switzerland) was approved in 1989 for treating CMV retinitis in AIDS patients. To circumvent the risks and inconvenience associated with the use of an indwelling catheter for IV administration, an oral formulation was developed. Oral ganciclovir represented a major advance in maintenance therapy and prophylaxis in case of CMV retinitis. However, the low bioavailability (approximately 5%) and the high pill burden from the TID regimen are significant limitations. Based on the model exemplified by valacyclovir, a prodrug was developed to improve the bioavailability of oral ganciclovir. Valganciclovir has an oral bioavailability of around 60%. It was approved in 2000 for the treatment of CMV retinitis in AIDS patients and was later approved for the prophylactic treatment of CMV in certain SOT recipients. Once-daily oral administration of valganciclovir 900 mg provides systemic exposure to ganciclovir that is equivalent to that provided by once-daily administration of IV ganciclovir 5 mg/kg. Besides systemic ganciclovir, intravitreal injection/implant of ganciclovir in the affected eye is also significantly efficacious in treating CMV retinitis. The elimination half-life of ganciclovir from the vitreous humor after intravitreal injection was estimated to be 13.3 hours in CMV retinitis patients. Intravitreal ganciclovir concentrations were estimated to remain above the ID_{50} (average 0.66 μg/mL) of the virus for about 62 hours after a single 200 μg intravitreal dose.[20] In clinical practice, injections are given two or three times per week during the induction phase, followed by once a week injections during long-term maintenance therapy. Frequent intravitreal injections appear to be a burden, as exemplified by the hesitation of the patient in our case. Patients treated with an intravitreal injection and implant alone are also at a significantly greater risk of developing CMV disease in the contralateral eye or in other organs.[21]

Although CMV retinitis patients, especially those with only midperipheral lesions, have shown a good response to IV ganciclovir or oral valganciclovir treatment, complicated macular and papillary lesions have less favorable prognosis with these formulations according to current studies.[12–15] Previous results have shown that ganciclovir alone is less effective for CME in CMV retinitis probably because of the high inflammatory component of CME. CME can even developed in the setting of resolving CMV retinitis in non-AIDS patients.[14] It also causes vision loss as a result of immune-recovery syndrome in HIV patients with a history of CMV retinitis on highly active antiretroviral therapy.[15] Our patient's hemograms showed relative immunocompetence during the ocular disease course. It is likely that he delayed seeking medical help until severe visual impairment occurred, when he was under an immune reconstitution status. Intravitreal injection of steroids seems a reasonable approach to treat the inflammation associated with macular edema and papillitis in CMV retinitis. However, CMV reactivation is a big concern.

MTX is a competitive inhibitor of dihydrofolate reductase. It has immunomodulatory and antiproliferative (antineoplasm) properties through multiple mechanisms. One of its major anti-inflammatory actions is inhibition of aminoimidazole carboxamide ribonucleotide transformylase/IMP cyclohydrolase resulting in increased intracellular and extracellular adenosine, which is a potent inhibitor of inflammation and modulates cell trafficking.[22] Adenosine also suppresses the action of proinflammatory mediators tumor necrosis factor-α, interleukin (IL)-6, IL-8, macrophage inflammatory protein-1α, leukotriene B4, and nitric oxide, and enhances the production of the anti-inflammatory mediators IL-10 and IL-1 receptor antagonists. Ultimately, adenosine leads to the resolution of inflammation by downregulating macrophage activation and promoting a shift from a T_H1 to a T_H2 response.[23] Systemic MTX has been included in many standard treatments for a variety of malignancies.[24] It is also a commonly used steroid-sparing agent for the treatment of systemic inflammatory disorders, such as systemic lupus erythematosus, rheumatoid arthritis, psoriasis, and a range of noninfectious uveitides.[25] Various ophthalmic inflammatory conditions response to intravitreal MTX therapy, and intraocular lymphomas associated with primary central nervous system lymphoma have been effectively and safely treated with intravitreal injections of MTX. A 400 μg concentration of MTX in human eyes appears to be clinically well tolerated.[26] The half-life of MTX in vitreous fluid was estimated to be 12.4–21.5 hours by assuming first-order elimination kinetics. Although the concentration was still high 24 hours after intravitreal injection (69.94–82.89μM), there was no ocular toxicity. A single intravitreal injection of 400 μg of MTX yielded antineoplasm levels in the vitreous for more than 72 hours.[27] A MTX 400 μg/0.1 mL weekly injection is universally applied in eyes with primary intraocular lymphoma. Moreover, in eyes with uveitis and CME, a single or few injections are highly curative. A study documented 76% control of inflammation and 56% corticosteroid-sparing effect in patients with various ocular inflammatory conditions treated with MTX.[28] Hardwig et al reported retention of visual acuity in 12 of 16 study eyes with conditions other than primary intraocular lymphoma after one single injection.[29] Taylor et al reported that 67% (10/15) of patients with uveitic CME responded to treatment at 1 month and 87% (13/15) by 3 months after one single injection. The median time to relapse was 4 months.[30] In our patient, the macular edema in OD responded rapidly to weekly intravitreal MTX 400 μg/0.1 mL injections for 1 month compared with the other eye, mainly due to the anti-inflammatory action and downregulation of macrophage activation by MTX. Moreover, the papillitis also underwent remission, although this might have been achieved by the induction treatment of oral valganciclovir alone.

The macular edema in OD did not recur after four intravitreal injections of MTX, while that in the OS persisted during the 8-month follow up. No ocular side effects were observed in the MTX-injected eye. Our case revealed the possible efficacy and safety of MTX as a corticosteroid-sparing adjuvant intravitreal injection in combination with valganciclovir (which has high oral bioavailability) for macular edema and for improving visual acuity. Further studies are needed to confirm our results.

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