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Treatment of Cytomegalovirus (CMV) Retinitis with CMV-Specific T-Lymphocyte Infusion

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Abstract

Cytomegalovirus (CMV) retinitis is a blinding infection that affects immunocompromised patients who are unable to generate a T-cell response against the organism. Infusion of CMV-specific leukocytes has been shown to be effective in patients with systemic CMV infection, especially those resistant to standard therapies. We report a case of a patient with CMV viremia with retinitis in whom infusion of third-party donor derived CMV pp65-specific T-cells alone prompted resolution of CMV retinitis in this patient. This case suggests a potential role for CMV-specific leukocyte infusion in the treatment of CMV retinitis, especially in cases resistant to or refractory or antiviral therapies.

Cytomegalovirus (CMV) retinitis typically afflicts patients who are unable to generate a T-cell response against the virus. Studies have demonstrated efficacy of CMV-specific leukocyte infusion for systemic CMV infection.[1-2] We report a case of CMV retinitis treated with infusion of third-party donor derived CMV pp65-specific T-cells.

Case Report

The patient is a 26 year old male with a history of pre-B-cell acute lymphoblastic leukemia status post allogeneic stem cell transplant (SCT) on immunosuppressive therapy for graft-versus-host disease (GVHD). One year prior to presentation, he developed CMV viremia and esophagitis which were treated with valganciclovir for one year, then changed to intravenous foscarnet two months earlier for worsening viremia and dysphagia. At that time all systemic immunosuppressive therapy was discontinued except imatinib maintainance

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therapy for leukemia. One week before presentation, leflunomide was started to treat worsening viremia since the CMV mutations in UL54 conferred resistance to foscarnet, cidofovir, and ganciclovir.

The patient reported blurry vision in the left eye. On presentation, visual acuity (VA) was 20/20 OD and 20/25 OS. Fundoscopy revealed vision-threatening CMV retinitis OU (Figure 1A,B). Biweekly intravitreal ganciclovir injections (2mg/0.1mL) were administered 3 times OD and 4 times OS, with worsening retinitis OD and modest response in retinitis OS (Figure 1C,D). His CMV viremia, however, continued to worsen.

Given the limited therapeutic options remaining for his *systemic* infection, antiviral therapy was discontinued and the patient was treated with third-party donor derived CMV pp65-specific cytotoxic T-cells (CMVpp65 CTLs). The CTL line was generated under good manufacturing practice conditions and met clinical release criteria as previously described.[3] The CMVpp65 CTLs were HLA -matched to the recipient and his stem cell donor at 3 of 8 alleles at high resolution and were restricted in their cytotoxicity to CMV epitopes presented by HLA A0201.

He underwent 3 weekly infusions of 1×10^6/kg CMVpp65 CTLs, followed by a 2 week break, and then 3 additional weekly infusions. No system antiviral nor intravitreal antivirals were administered. Retinitis completely resolved and remained inactive during the 3 month follow-up (Figure 1E-H). VA improved from 20/40 OU at 1 day following T-cell infusion to 20/25+ OD and 20/40+ OS at 3 month follow-up visit. The CMV viral load remained undetectable without antiviral therapy during the follow-up period. CMV CTL precursors were subsequently demonstrated to have expanded in the peripheral blood. There was no worsening of his systemic GVHD during treatment. CMV retinitis continued to be clinically stable for months after cessation of CMV-specific leukocyte infusion, at which point the infused leukocytes would be expected to be “rejected” from the system given the partial HLA-matching.

Discussion

CMV is a member of the herpes viral family and is thus composed of double stranded DNA enclosed by an icosahedral protein capsid, which in turn is surrounded by a lipid bilayer envelope.[3] It is thought that viral particles in the blood enter retinal vascular endothelial cells through endocytosis, resulting ultimately in disruption of the blood-retinal barrier and access thereafter to the retinal tissues.[4-5] CMV retinitis general begins peripherally and spreads centrifugally, with profound visual loss occurring when the infection spreads to the macula or nerve, or when peripheral retinitis leads to a retinal detachment that extends to the macula.

CMV retinitis occurs in patients who are unable to generate a T-cell response against the virus, including patients with acquired immunodeficiency syndrome or patients on potent immunosuppressant therapy, such as with malignancies or after solid organ transplantation, especially with transplantation of a CMV-positive organ into a CMV-negative patient. In

patients undergoing allogenic SCT, the risk is particularly high with a CMV-negative donor and CMV-positive recipient and/or in the setting of immunosuppressants for GVHD.[4-5]

Treatment of CMV retinitis focuses upon antiviral agents, as well as reconstitution of the immune system, whether by recovery of blood counts after immunosuppression or transplant or antiretroviral therapy in patients with AIDS. Systemic antivirals employed against CMV include gancyclovir, valganciclovir, cidofavir, foscarnet, or leflunomide, though development of resistance is not uncommon.[6-7] The patient reported here developed resistance of his CMV viremia to antiviral therapy. Moreover, persistent CMV infection despite engraftment of his bone marrow and cessation of all immunosuppressants suggested a functional deficit of CMV-specific leukocytes. He therefore underwent infusion of matched third-party derived CMV pp65-specific cytotoxic T-cells for CMV viremia. During this time, he received no antivirals either systemically or intravitreally and exhibited prompt stabilization and resolution of his CMV retinitis as well.

Studies have demonstrated efficacy of CMV-specific leukocyte transfusion for systemic CMV.[1-2] There is also one report in the literature of a patient with a history of SCT for leukemia, who developed CMV retinitis which was treated with systemic ganciclovir and foscarnet, and donor leukocyte infusion. Leukocyte infusion was implicated in the resolution of CMV retinitis, but the concurrent effect of systemic ganciclovir and foscarnet could not be ruled out.[8] In contrast, our patient was treated with CMV-specific leukocyte infusion alone with full resolution of the retinitis and viremia.

We report the first case of CMV retinitis successfully treated with CMVpp65 CTL infusions. Given the complexity and highly specialized nature of this therapy, however, these infusions might best be reserved for those patients refractory or resistant to intravitreal and systemic antiviral therapies. While the patient reported here exhibited systemic resistance to antivirals, it is possible that the high concentrations of antivirals achievable from intravitreal injections may have been efficacious for his CMV retinitis. Further studies are therefore necessary to determine whether this treatment modality may be applicable to the population of patients whose CMV retinitis responds poorly to aggressive systemic and intravitreal antiviral therapy.

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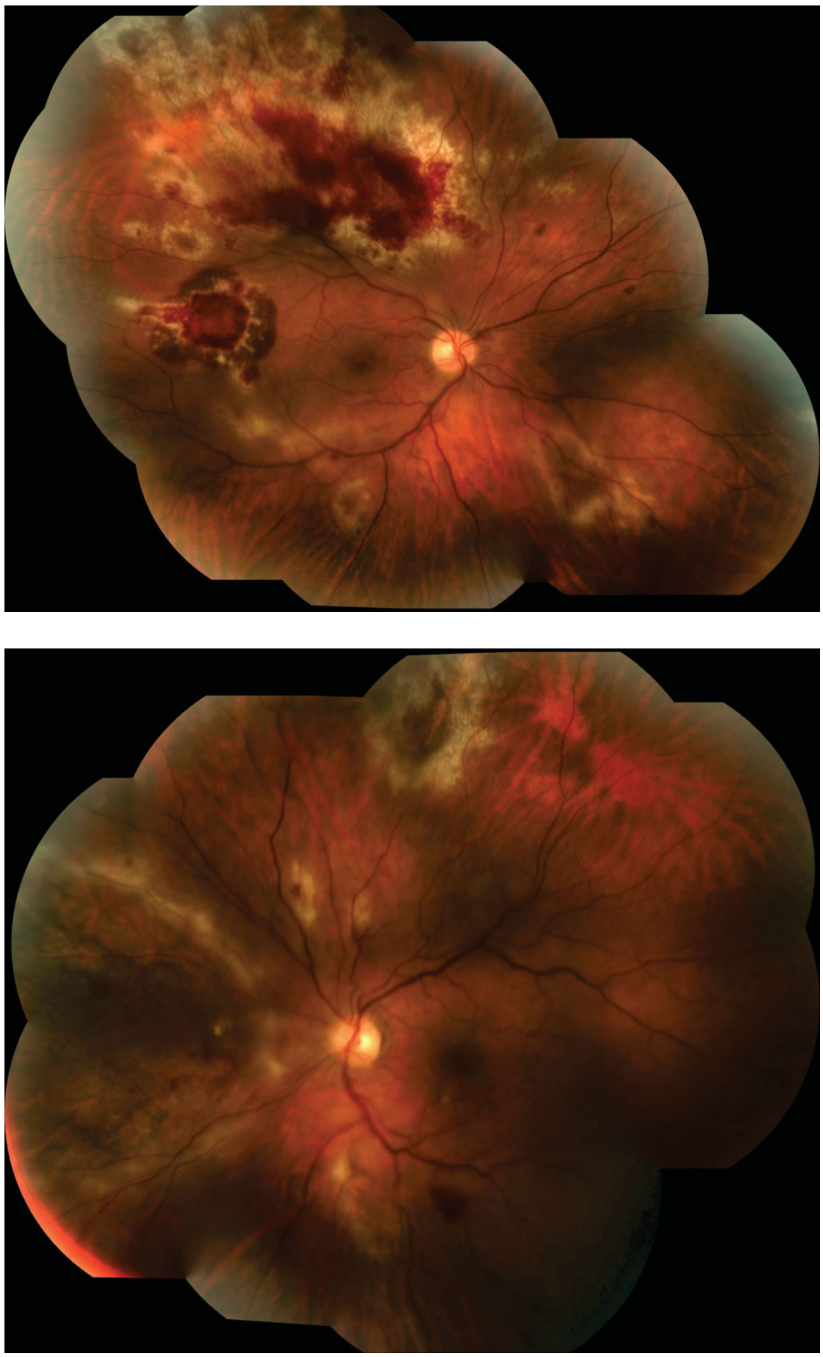

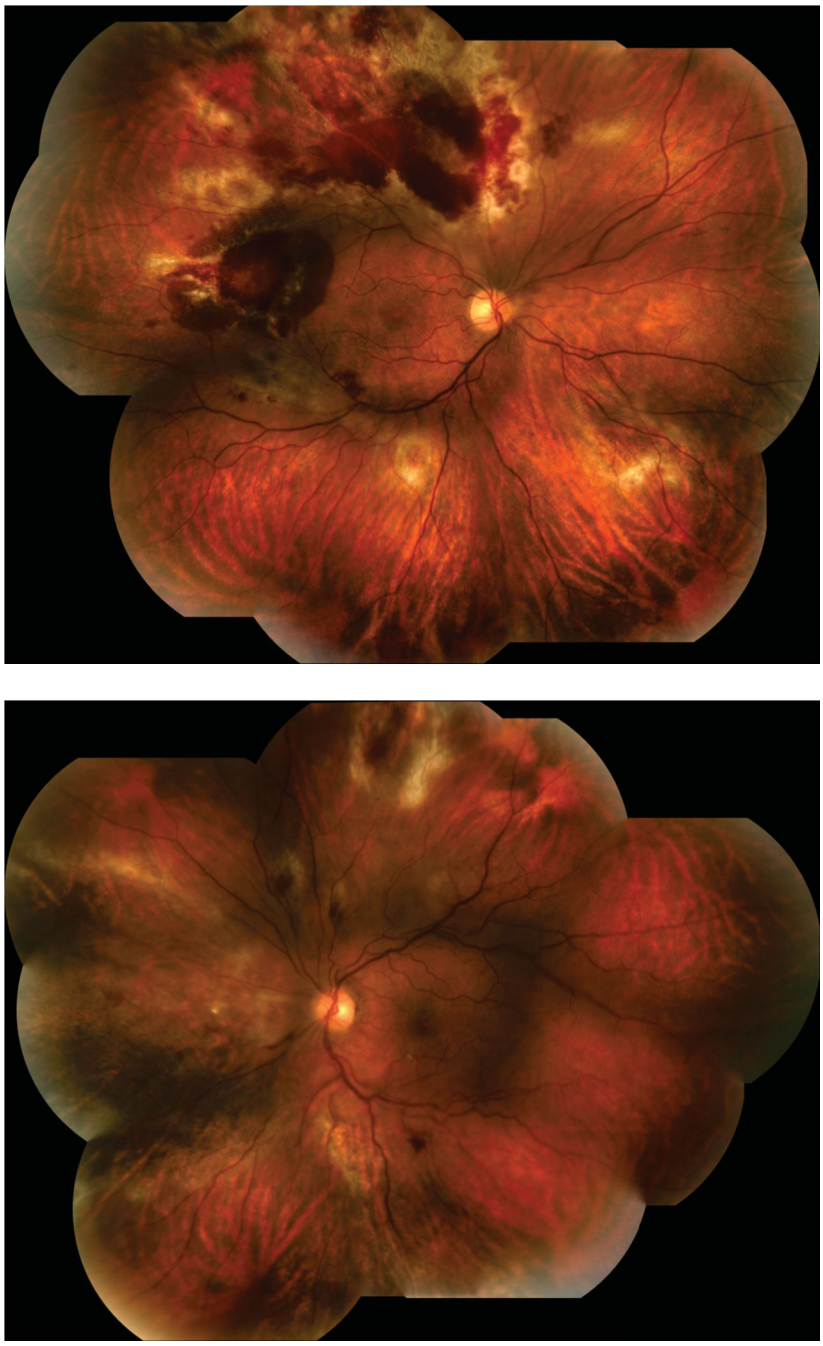

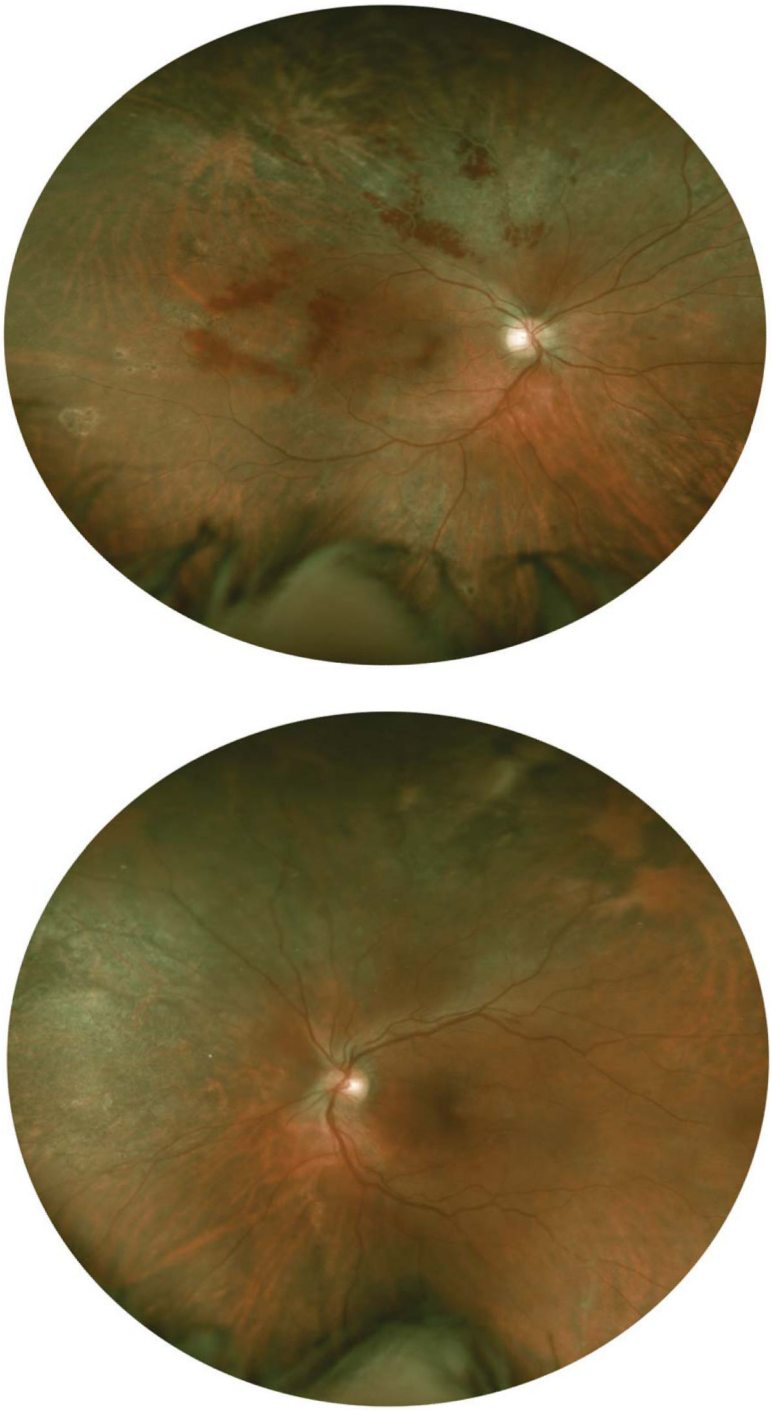

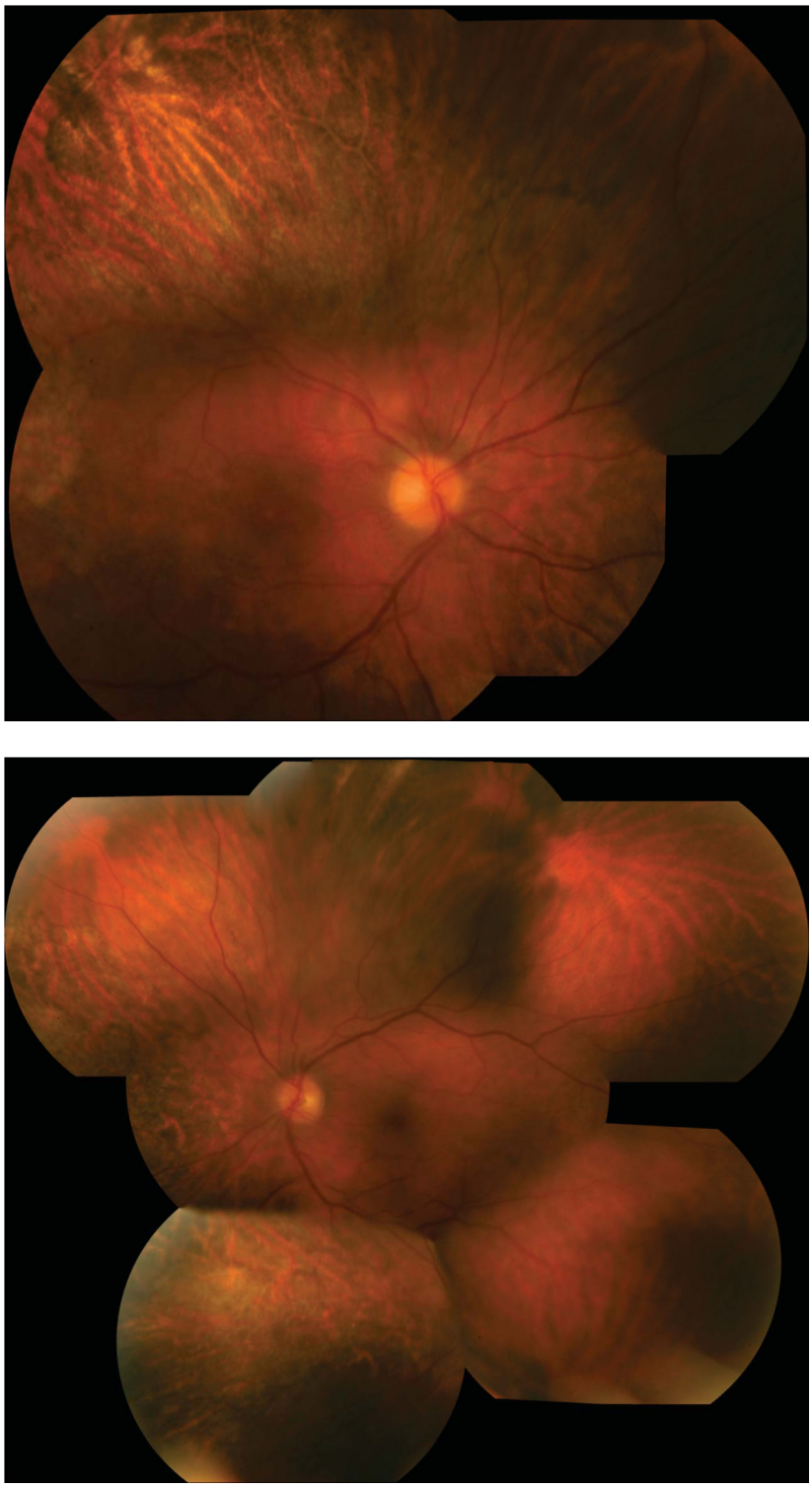

Figure 1.
Fundus photography showing new active cytomegalovirus retinitis OU at presentation (A,B). At 2 week follow-up after biweekly intravitreal ganciclovir injections in both eyes, some worsening retinitis is noted OD (C) with minimal improvement OS (D). Fundus

photography six weeks later, after two rounds of three cycles of CMV-specific T-cell infusion, showing marked consolidation with almost complete resolution of any areas of active retinitis (E,F). Fundus photography at 3 month follow-up showing completely inactive retinitis off antiviral therapy (G,H).