

# Cytomegalovirus Retinitis after Intravitreal Bevacizumab Injection in an Immunocompetent Patient

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We report a case of cytomegalovirus (CMV) retinitis after intravitreal bevacizumab injection. A 61-year-old woman with diabetic macular edema developed dense vitritis and necrotizing retinitis 3 weeks after intravitreal bevacizumab injection. A diagnostic vitrectomy was performed. The undiluted vitreous sample acquired by vitrectomy was analyzed by polymerase chain reaction and culture. Polymerase chain reaction of the vitreous was positive for CMV DNA. Other laboratory results did not show evidence of other infectious retinitis and systemic immune dysfunction. Human immunodeficiency virus antibodies were also negative. After systemic administration of ganciclovir, retinitis has resolved and there has been no recurrence of retinitis during the follow-up period of 12 months. Ophthalmologists should be aware of potential risk for CMV retinitis after intravitreal bevacizumab injection.

**Key Words:** Bevacizumab, Cytomegalovirus, Retinitis

Cytomegalovirus (CMV) infections are usually asymptomatic or cause a benign, self-limited course in immunocompetent patients. Various ocular manifestations related with intraocular CMV infection could be shown in healthy patients including mild self-limiting iritis with sector iris atrophy [1], corneal endotheliitis [2] and anterior uveitis [3,4]. Severe life-threatening CMV infections are known to present in immunocompromised patients such as those with advanced acquired immune deficiency syndrome, transplant recipients and those taking immunosuppressant therapy. In immunocompetent adults, severe CMV infections are rare but CMV reactivation might induce several diseases. The prevalence of systemic disease due to CMV was reported in up to 1.6% in immunocompetent adults including hepatitis and colitis [5,6]. Among the intraocular manifestations, CMV retinitis is a sight-threatening, op-

portunistic infection that has been documented in immunocompromised patients [7,8]. It is believed that CMV retinitis is extremely rare in immunocompetent patients, but several exceptional cases of CMV retinitis were reported after an intravitreal injection of triamcinolone [9-11] or fluocinolone acetonide (Retisert; Bausch & Lomb, Rochester, NY, USA) implants [12]. The authors suggest that local immunosuppression might promote replication of CMV and lead to retinitis. Herein, we report a case of CMV retinitis in an immunocompetent patient after an intravitreal injection of bevacizumab without the evidence of systemic or local immunosuppression.

## Case Report

A 61-year-old woman with well controlled diabetes visited our clinic in March 2009 for ocular pain and visual impairment of the left eye persisting for 2 weeks. In another clinic, she had been diagnosed with proliferative diabetic retinopathy of both eyes and cystoid macular edema of the left eye. She had received an intravitreal injection of bevacizumab (Genentech, San Francisco, CA, USA) in the left eye 3 weeks prior and panretinal photocoagulation in both eyes 2 weeks before her visit to our clinic. After treatment,

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she had used an anti-glaucoma agent because of increased intraocular pressure of the left eye.

At presentation, vision of the left eye was hand motion only. Slit lamp examination demonstrated 4+ cells and hyphema in the anterior chamber and iris neovascularization. Funduscopy revealed dense vitritis and retinal vascular obliteration. Ocular ischemia was suspected through fluorescein angiography which revealed arterial filling delay. No abnormal findings were observed in carotid Doppler sonography which was performed to rule out ocular ischemic syndrome. Examination of the right eye was unremarkable except diabetic retinopathy and scarring from panretinal photocoagulation. Further detailed examination was needed to draw the diagnosis and treatment plan but dense vitritis disturbed further evaluation. As a result, a pars plana vitrectomy was performed. During the vitrectomy, necrotizing retinitis with dense retinal whitening and hemorrhage along the inferotemporal vascular arcade was observed, suggestive of infectious retinitis (Fig. 1). The undiluted vitreous sample acquired by vitrectomy was analyzed by polymerase chain reaction (PCR; Q-CMV real time complete kit, Nanogen Advanced Diagnostics, Turin, Italy) and cultured for herpes simplex virus (HSV), varicellar zoster virus (VZV), and CMV. To rule out other etiologies of infectious retinitis, vitreous was also analyzed by staining and culture for bacteria and fungus.

Blood tests did not show any immune dysfunction and complete blood count was normal. CD4 and CD8 cells counts were also within the normal range, 522 and 275 cells/ $\mu$ L. Human immunodeficiency virus (HIV) antigen and antibodies were negative. Her serum CMV IgG level was 244.5 units (range of nonreactive <6.0 AU/mL) and IgM was negative. Although the CMV antigenemia test showed positive results (9/20,000 cells) using the Biotest CMV Brite kit (Biotest Diagnostics, Denville, NJ, USA),

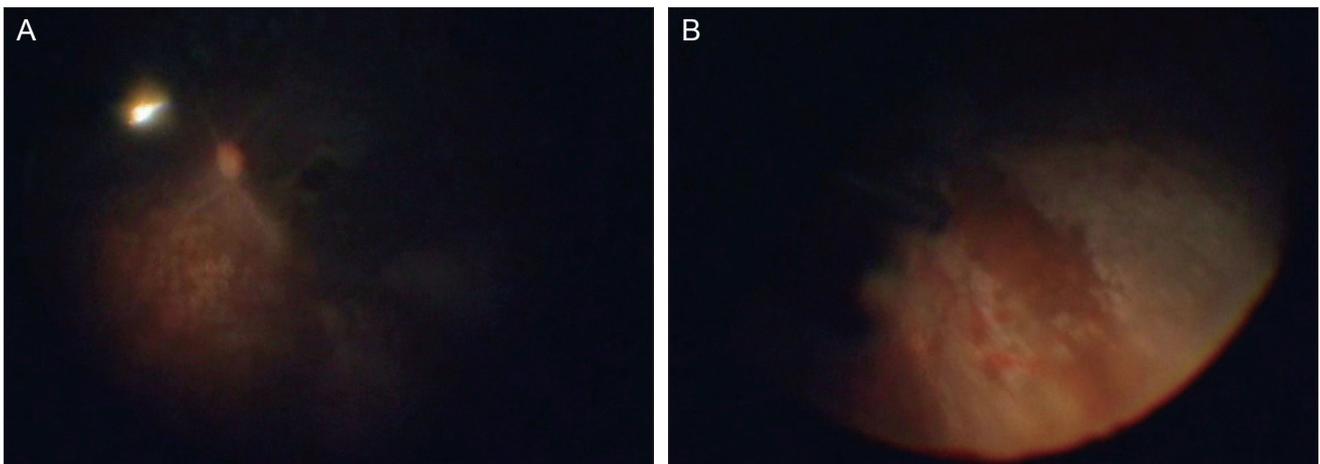
there were no other clinical manifestations of CMV infection except retinitis.

While the culture for CMV was negative, PCR for CMV DNA was positive in the vitreous and negative in peripheral blood, confirming the diagnosis as CMV retinitis. The others including HSV and VZV were negative in the vitreous and blood. Neither bacteria nor fungus were observed by staining and culture.

The patient underwent intravenous administration of ganciclovir (2.5 mg/kg/12 hr), a half dose reduction because of renal insufficiency. Necrotizing retinitis with retinal whitening and iris neovascularization had markedly decreased, but obliterated vessels were sustained without recovery of nonperfusion. After 17 days of administration, intravenous treatment was discontinued. During the follow-up period of 12 months, there has been no recurrence of retinitis, but her left eye could not perceive light because of optic nerve atrophy and retinal ischemia due to obliteration of retinal vessels.

## Discussion

While CMV retinitis is a well-known opportunistic infection usually affecting immunocompromised patients, there have also been reports of CMV retinitis in immunocompetent patients after intraocular steroid injection [9-11] or fluocinolone acetonide (Retisert) implant [12]. Recent reports revealed CMV retinitis after intravitreal bevacizumab injection combined with subtenon steroid injection [13]. Although the mechanism of CMV retinitis in immunocompetent patients is unclear, these reports suggested the immunosuppressive effect of steroids might provoke the reactivation of latent CMV. However, unlike steroids, bevacizumab, which was used in this case, has no immunosuppressive effects.



**Fig. 1.** Fundus photograph of left eye taken during pars plana vitrectomy. Note the retinal vascular obliteration (A) and inferotemporal confluent necrotizing retinitis associated with retinal whitening (B). Inferior panretinal photocoagulation burns are also can be seen.

In this case, fundus examination during vitrectomy revealed a necrotizing retinitis with retinal opacification, but several findings were not compatible with typical CMV retinitis such as severe reactions of the anterior chamber with iris neovascularization and retinal vascular obliteration. The possible explanation for those findings is deterioration of ischemic changes caused by superimposed diabetic retinopathy.

To rule out the accompanying active systemic CMV infection, we conducted the following tests; quantitative PCR in the plasma, antigenemia assay in peripheral blood leukocyte and cultures of peripheral blood and urine. The only test showing positive results was the antigenemia assay; all others were negative. However, antigenemia is a semi-quantitative assay and quantitative measurements by quantitative PCR might be more reliable for diagnosis of active CMV disease. PCR using plasma detects only free virion indicative of active viral replication with a higher clinical relevance as compared with antigenemia assay using leukocytes [14,15]. Except for CMV retinitis, the patient did not show clinical manifestations of systemic CMV diseases according to standard criteria [16] at the time of examination and during the follow-up period. Also, there was no evidence of abnormalities in the systemic immune system. After considering these findings, we reached the conclusion that she had no active systemic CMV infection other than CMV retinitis and retinitis was strongly suspected to correlate with the bevacizumab injection. Disruption of blood retinal barrier by diabetic retinopathy might play a role on the development of CMV retinitis [17], but the pathogenesis of CMV retinitis after bevacizumab injection is still unclear. The authors hope this case can promote awareness of the risk of CMV retinitis and the need for close monitoring for a considerable period after intravitreal bevacizumab injection.

## Conflict of Interest

No potential conflict of interest relevant to this article is reported.

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