Fibrovascular Changes Misdiagnosed as Cytomegalovirus Retinitis Reactivation in a Patient with Immune Recovery

Michael R. Robinson,† Karl G. Csaky,‡ Susan S. Lee,‡ Henry Masur,‡ and Michael A. Polis§
†National Eye Institute and ‡National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

A patient with human immunodeficiency virus infection and cytomegalovirus (CMV) retinitis developed immune recovery uveitis as a result of receipt of highly active antiretroviral therapy. Fibrovascular changes occurred in the CMV retinitis scar, were misdiagnosed as CMV retinitis reactivation, and were treated with anti-CMV medication. Fibrovascular membranes can be misdiagnosed as reactivated CMV retinitis, and a proper diagnosis is essential to avoid unnecessary therapy with potentially toxic antiviral medications.

Immune recovery uveitis (IRU) is an ocular inflammation associated with cytomegalovirus (CMV) retinitis in patients with immune recovery due to HAART [1–4]. IRU is associated with vitreous inflammation and macular edema that leads to vision loss [2]. Ocular neovascularization at the optic disc and the retinal periphery also occurs in patients with IRU [5–8]. Herein, we describe a patient with misdiagnosed progressive fibrovascular changes who was treated for CMV retinitis reactivation.

Case report. A 41-year-old man received a diagnosis of HIV infection in 1991 and developed bilateral CMV retinitis in 1993. He was initially treated with intravenous foscarnet for 6 months, and, after progression of the retinitis, he was treated with intravenous ganciclovir until February 1996. The retinitis progressed, and intravenous cidofovir was administered for 2 months in 1996 but was discontinued because of a significant elevation in liver function test values. Intravenous ganciclovir therapy was restarted at an increased maintenance dose (8 mg/kg q.d.) and was continued until July 1997. The patient started receiving HAART (including lamivudine, stavudine, didanosine, and nelfinavir) in February 1997, and his CD4+ T lymphocyte count increased from 6 to 448 cells/μL during a 6-month period. Cataract surgery in the right eye with an intraocular lens implant was performed in April 1997.

The patient was initially examined at the National Eye Institute (NEI; Bethesda, MD) in May 1997; CMV retinitis had been inactive for the past year. The patient’s CD4+ T lymphocyte count was 183 cells/μL. His best-corrected visual acuity was 20/50 for the right eye and 20/40 for the left eye. The eye examination findings were significant for a posterior chamber implant in the right eye, posterior subcapsular cataract in the left eye, and 1+ vitreous cells in both eyes. CMV retinitis was inactive in both eyes. In July 1997, he was enrolled in the NEI protocol 97-EI-0081, in which specific anti-CMV medications were discontinued for patients with immune recovery resulting from HAART (CD4+ T lymphocyte count, ≥150 cells/μL). Intravenous ganciclovir therapy was discontinued, and the patient was reexamined monthly.

In November 1997, the patient complained of poor vision and increased floaters in both eyes. His best-corrected visual acuity was 20/100 for the right eye and 20/63 for the left eye. Examination revealed an increase in the vitreous inflammation in both eyes, and bilateral macular edema was documented by fluorescein angiography. To treat the increase in his immune recovery–related ocular inflammation, periocular dexamethasone phosphate (4 mg) was injected into the right eye, and topical eye drops (prednisolone acetate 1% and ketorolac trometamol) were prescribed for use in both eyes. Long-acting corticosteroid depot preparations, such as triamcinolone acetonide, were not used clinically until 1999, because it was not known whether this would cause reactivation of CMV retinitis.

In December 1997, vision worsened in the patient’s right eye (to only counting fingers), and clinical examination revealed increased vitritis and severe macular edema. The CD4+ T lymphocyte count was 192 cells/μL. Vision in the left eye was stable, at 20/50 with mild macular edema. The patient started prednisone therapy (60 mg q.d.), with a taper in the schedule over the subsequent 4 weeks. In January 1998, after completing the course of prednisone, the visual acuity had improved in the right eye to 20/100 and in the left eye to 20/40. Another injection of periocular dexamethasone phosphate (4 mg) was administered in the right eye in February 1998, with no significant improvement in vision.

The posterior subcapsular cataract in the left eye was removed in March 1998, and the patient had an uneventful post-
operative course. The patient’s visual acuity in May 1998 was 20/125 in the right eye and 20/25 in the left eye, with macular edema present clinically in the right eye and a low-grade vitritis (trace to 1+ cells) present in both eyes. To reduce the inflammatory precipitates depositing on the intraocular lens implant, topical prednisolone acetate 1% eye drops were administered in both eyes 1–8 times per day during the period of May 1998 to March 2001 and 2 times per day from March 2001 to August 2003 (the last examination date). The visual acuity decreased in the right eye to 20/250 in November 1998 as a result of increased macular edema, and another injection of periocular dexamethasone phosphate (4 mg) was administered. From December 1998 to August 2000, the patient had low-grade vitritis in both eyes, chronic macular edema in the right eye, and visual acuity ranging from 20/50 to 20/100 in the right eye and 20/25 to 20/40 in the left eye. CMV retinitis remained inactive, with no signs of reactivation, such as areas of retinal necrosis and hemorrhage at the leading edge of the CMV retinitis scar.

The patient developed white tissue in the CMV retinitis scar in the right eye in August 2000; this had not been present on previous retinal photographs (figure 1A and 1B). Retinal angiography was not possible because of an allergy to fluorescein, but clinical examination with magnification revealed that these lesions were fibrovascular membranes. There were no signs of CMV retinitis reactivation, with an absence of retinal whitening and necrosis at the leading edge of a CMV retinitis scar. From August 2000 to July 2002, a fibrovascular membrane developed along the leading edge of the CMV retinitis scar in the left superior macula, but the membranes in the right eye remained unchanged. During this period, the visual acuity ranged from 20/80 to 20/125 in the right eye and 20/25 to 20/40 in the left eye, with no change in the vitritis or macular edema in the right eye. During the period of August 2001 to July 2002, the patient’s CD4+ T lymphocyte count was 168–252 cells/µL, with a count of 222 cells/µL documented in July 2002. His HIV load was undetectable from August 2001 to July 2002.

On a routine office visit with an outside ophthalmologist in September 2002, the patient received a diagnosis of reactivation of CMV retinitis in the right eye when new areas of white tissue were observed over the CMV retinitis scar. The patient received oral valganciclovir for 3 months and was referred back to the NEI when there was no clinical response. The patient was reexamined in January 2003 at the NEI. Visual acuity was found to be stable (20/125 in the right eye and 20/40 in the left eye), and the CD4+ T lymphocyte count was stable at 219 cells/µL; the HIV load was undetectable. Examination revealed no areas of CMV reactivation in the retina, but new areas of fibrovascularization were present (figure 1C). These new areas of fibrovascularization had likely been misinterpreted by the outside ophthalmologist as reactivation of CMV retinitis. Valganciclovir therapy was discontinued, and a reexamination in August 2003 revealed no significant changes in vision or the CD4+ T lymphocyte count. The fibrovascular membranes in both eyes remained unchanged, CMV retinitis was inactive, and there were no clinical changes in the vitritis or the macular edema in both eyes.
Discussion. We initially described extensive peripheral fibrovascular membranes occurring at the leading edge of CMV retinitis scars as a later manifestation of IRU [8], but this appears to occur infrequently, because there have been no other reports in the literature. Common manifestations of IRU that typically develop soon after the initiation of HAART include a mild anterior uveitis, vitritis, optic disc edema, and macular edema [1–4]. Complications of chronic inflammation in these patients include cataract and epiretinal membrane formation [2]. The most important cause of vision loss in these patients is macular edema, for which there are no treatment approaches that have led to durable responses in the majority of the patients.

Distinguishing between reactivation of a CMV retinitis scar and fibrovascular membranes can be difficult. Factors that help distinguish between the 2 items include the relatively slow rate that fibrovascular membranes progress and the fine vessels that are visible in the fibrovascular lesions. In addition, the fibrovascular membranes are not associated with areas of necrosis and hemorrhage that would suggest CMV retinitis reactivation. Reactivation can occur in patients with immune recovery, but it generally follows a decrease in the CD4+ T lymphocyte count to <50 cells/μL [9], although rare cases of active CMV retinitis occurring in patients with apparent immune recovery and CD4+ T lymphocyte counts of >200 cells/μL have been reported; in these cases, repopulation of CD4 T cell clones specific to CMV did not occur [10].

The etiology of the fibrovascular changes in the absence of retinal nonperfusion is not known but may be related to vascular endothelial growth factor expression, which occurs in patients with chronic uveitis and in experimental models [11]. Immunostaining of similar fibrovascular membranes removed from patients with IRU for retinal detachment repair has revealed numerous CD4+ T lymphocytes [12]. The presence of T lymphocytes in the retina has been also seen in patients with other retinal fibrovascular diseases, such as the subretinal fibrosis and uveitis syndrome [13]. The pathogenesis of fibrovascular membrane formation in patients with IRU may be hard to elucidate, because it is relatively uncommon and because surgically obtaining tissue specimens is not justified if the membrane follows a benign clinical course. Specific therapy for these fibrovascular membranes is not required unless they lead to recurrent vitreous hemorrhages and vision loss [8]. However, proper diagnosis is essential to differentiate fibrovascular lesions from CMV retinitis reactivation and to avoid administering unnecessary therapy with potentially toxic antiviral medications. Retinal fibrovascular changes can also occur in patients with systemic diseases, such as diabetes mellitus and sickle cell disease, and appropriate laboratory testing is recommended when evaluating these patients.

In spite of the remarkable decreases in morbidity associated with the use of HAART in persons with advanced HIV infection, the manifestations of immune recovery in persons with a history of CMV retinitis require close and continued attention by an ophthalmologist familiar with the disease.

References