ABSTRACT

Cytomegalovirus (CMV) retinitis after heart transplantation is well documented, but few cases of central retinal vein occlusion (CRVO) have been described in these patients. A man seropositive to CMV antigen after heart transplantation received prophylactic ganciclovir therapy. Nevertheless, cytomegalovirus retinitis developed and CRVO was diagnosed in his other eye. Common risk factors for retinal vein occlusion were excluded. Cytomegalovirus infection may have played a role in the pathogenesis of CRVO.

CASE REPORT

Simultaneous Cytomegalovirus Retinitis and Central Retinal Vein Occlusion of a Heart Transplant Recipient

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Cytomegalovirus (CMV) retinitis after organ transplantation has been well documented,[1-4] and usually responds adequately to a short course of ganciclovir therapy. In contrast, when retinits affects patients with acquired immunodeficiency syndrome (AIDS), suppressive therapy for prolonged periods may be required.[5] Cytomegalovirus retinitis in heart transplant recipients is similar to that described for other organ transplantations.[3]

On the other hand, central retinal vein occlusion (CRVO) after cardiac transplant has been scarcely described in the literature.[6,7] We herein present the simultaneous presentation of CMV retinitis and CRVO in the fellow eye of a heart transplant recipient. The occurrence of CMV infection may have contributed to the development of CRVO in our patient.

Case Report

A 51-year-old man underwent successful orthotopic heart transplantation, performed because of refractory advanced idiopathic myocardiopathy. The patient had no peripheral vascular disease, hypertension, or diabetes mellitus before the transplant. Preoperatively, serologic testing for human immunodeficiency virus (HIV) was negative, and the IgG anti-CMV titer

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was 1/10,000. The donor organ came from a 34-year-old man, who was CMV seronegative. Cardiopulmonary bypass time was 60 minutes. The patient received fresh-frozen plasma during the intervention.

The immunosuppressive regimen included induction therapy with OKT3 (5 mg/day for 7 days). The patient also received concomitant administration of corticosteroids (deflazacort, 0.6 mg/kg/day), cyclosporine (5 mg/kg/day for a level of 200 to 300 ng/mL assessed by radioimmunoassay and started on postoperative day 4), and azathioprine (3 mg/kg/day to maintain a total white blood cell count of at least 4000 cells/mm^3, started 10 days after surgery).

According to our hospital's post-transplantation protocol, the patient underwent periodical assays for CMV antigen detection and blood cultures for CMV. By postoperative day 15, these assays and cultures became persistently positive. Although the patient remained asymptomatic, he was admitted to the hospital 3 months after the transplant in an attempt to achieve negative CMV antigen detection. He was treated with intravenous ganciclovir sodium (6.5 mg/kg/day for 3 weeks), followed by oral ganciclovir therapy (1000 mg 3 times a day). Nevertheless, CMV antigen positivity persisted.

Five months after the transplant, the patient noted decreased vision in his left eye. He was still receiving oral ganciclovir (1000 mg 3 times a day). Best-corrected visual acuity was 20/20, right eye, and 20/70, left eye, with a correction of –0.50 –0.50 × 120 and –0.75 –0.50 × 60, respectively. The anterior segment findings were unremarkable. Intraocular pressures were 15 mm Hg in the right eye and 16 mm Hg in the left eye. The vitreous was clear bilaterally. Fundus examination revealed patches of retinitis in the inferior temporal quadrant of the right eye, with minor hemorrhages and perivenous sheathing (Fig 1A). In the left eye, widespread areas of retinal hemorrhage, affecting mainly the inferior retina, were seen (Fig 2). Fluorescein angiography of the left eye showed no signs of ischemia (Fig 3). A diagnosis of CMV retinitis in the right eye and CRVO in the left eye was made.

At diagnosis, his blood pressure was 110/70 mm Hg. Laboratory evaluation showed normal cholesterol and triglyceride levels. Glucose level was 89 mg/dL (normal range, 65 to 110 mg/dL). Hemoglobin level was 12.8 g/dL (normal range, 12 to 16 g/dL), with a hematocrit of 33.1% (normal range, 37% to 55%). The leukocyte count was 7.1 × 10^9/L with a CD4+ lymphocyte count of 366 cells/mm^3. The CD4/CD8 ratio at this time, 5 months after transplant, was 5.08, changing from 2.43, 2.21, and 3.64 at 1, 2, and 3 weeks, respectively, and 2.34 and 8.31 at 1 and 3 months, respectively. Platelet counts were normal. Rapid plasmin reagin, anticardiolipin antibody, and lupus anticoagulant were negative. Serum viscosity, serum complement concentrations, and fibrinogen concentrations were normal. Results of IgM anti-CMV detection were negative.

The patient was then treated with intravenous ganciclovir sodium (9 mg/kg/day). The dosages of immunosuppressive therapy were reduced as follows: deflazacort, 0.2 mg/kg/day; cyclosporine, 3.5 mg/kg/day (levels of 150 to 250 ng/mL); and azathioprine, 2 mg/kg/day.

Three weeks later, visual acuity remained the same in the right eye (20/20) and had decreased to 20/400 in the left eye. In the right eye, retinitis and hemorrhagic areas had decreased considerably, and opaque threads corresponding to occluded vessels, with resolution of the periphlebitis, could be seen (Fig 1B). In the left eye, a substantial decrease was seen in the amount of hemorrhages. Cytomegalovirus antigen detection and blood culture for CMV were negative. Because of the improvement in the ophthalmoscopic findings, maintenance therapy with oral ganciclovir (1000 mg 3 times a day) was started.

Seven weeks after diagnosis, visual acuity in the left eye had increased to 20/100. Visual acuity in the right eye remained stable, and complete resolution of retinitis was observed.

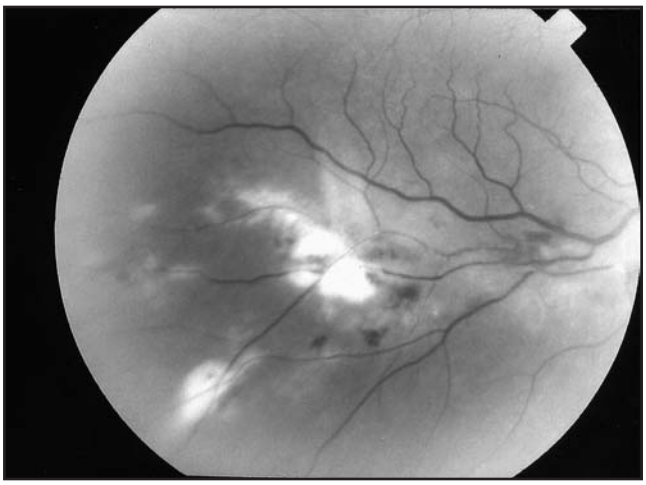

Fig 1A.—Fundus photograph of the inferior temporal quadrant of the retina of the right eye at diagnosis. Small areas of active retinitis are evident.

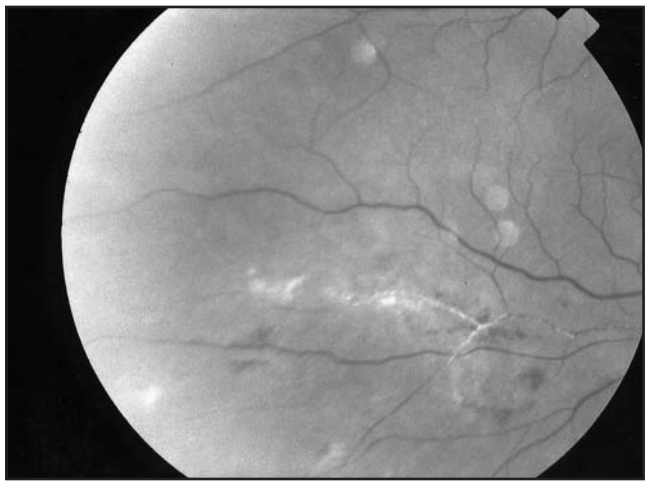

Fig 1B.—Fundus photograph of the inferior temporal quadrant of the retina of the right eye after 3 weeks of induction treatment. A substantial improvement can be observed. Note that the perivascular sheathing has disappeared.

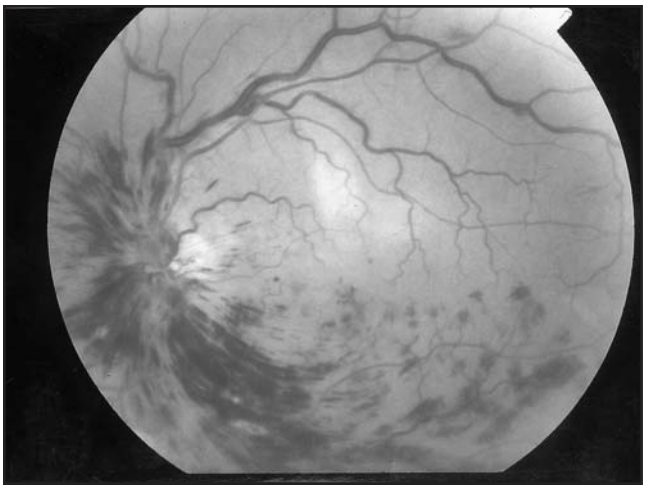

Fig 2.—Central retinal vein occlusion is observed in the left eye.

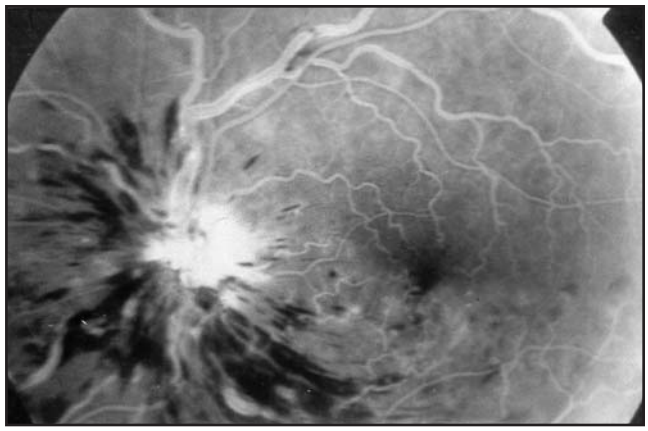

Fig 3.—Fluorescein angiogram of the left eye. The retinal capillary bed is well perfused, and no signs of ischemia are seen.

Discussion

Ocular complications after heart transplantation have been described in very few reports.[4,6-8] Quinlan and Salmon[7] found that lens changes related to prolonged oral corticosteroid therapy (in 43% of patients) and retinal vascular changes (37.3 %) were the 2 major complications. They described a 3.4% incidence of CMV retinitis during the first 6 months after heart transplant.[7]

Possible sources of CMV infection in transplant recipients are: (1) reactivation of a latent infection present before transplantation due to the immunosuppressive therapy and (2) primary infection transmitted through blood transfusion or via transplanted organs, particularly when seropositive organs are implanted in seronegatives recipients.[3] Since our patient was CMV seropositive before transplant, CMV infection was problably the result of immunosuppression secondary to drug therapy. However, blood transfusion or organ donor transmission cannot be completely ruled out in our patient, since it has been suggested that transmission of CMV from an organ donor can occur even in seropositive recipients.[9] Cytomegalovirus infections in recipients of a solid organ transplant, globally evidenced in two-thirds of these patients, have not been as severe as in bone marrow transplantation and in patients with AIDS.

Regarding the immunologic parameters, inverted CD4/CD8 ratios have been described as occurring about the same time as symptomatic CMV infection, and these ratios remain suppressed for the course of the infection.[10] However, this did not occur in our patient, as can be observed in the evolution of the CD4/CD8 ratio, mentioned in the Results. Evidence of the formation of IgM antibody to CMV has been detected in patients with both primary infection and in those with reactivation.[11] However, in our patient, IgM antibody CMV detection proved negative at the time of active infection.

Central retinal vein occlusion is thought to be secondary to the formation of a thrombus in the central retinal vein. There are several conditions that may contribute to thrombus formation. These include altered blood flow, alterations in blood viscosity, clotting factor abnormalities, and abnormalities of the vessel walls.[12] Common risk factors for CRVO (ie, diabetes mellitus, systemic arterial hypertension, hyperlipidemia, and hyperopia) were exhaustively ruled out in our patient. Laboratory workup showed no alterations in blood cell count, clotting factors, or blood viscosity. Other factors that may have contributed to the development of CRVO are related to the surgical procedure and immunosuppressive therapy.

Regarding the surgical procedure, a cardiopulmonary bypass is required in patients undergoing heart transplantation. Cardiopulmonary bypass has been shown to cause systemic hypotension and loss of the pulsatile component of blood flow.[13] In addition, platelets are frequently damaged, and complement activation with platelet aggregates may develop during the procedure.[14] Thus, cardiopulmonary bypass causes both blood flow and viscosity alterations. Nevertheless, this mechanism is an unlikely cause since venous occlusion ocurred a long time after surgery.

Concerning factors related to immunosuppressive therapy, OKT3 (ie, monoclonal antibody used in induction therapy) has been associated with a high occurrence of vascular thrombosis.[15] Furthermore, cyclosporine has been reported to cause damage to small vessels.[16]

It is known that endothelial cells play an active role in the control of the procoagulant-anticoagulant balance in blood. A displacement of this equilibrium leads to hemorrhage or thrombotic complications. It has been shown that CMV can proliferate in human endothelial cells.[17] Bruggeman et al[18] demonstrated that CMV infection induces a decrease in the cellular content of von Willebrand factor in infected cells. This factor, synthesized and released by endothelial cells, plays a role in the adhesion of platelets to the vessel wall. In addition, Hendrix et al[19] reported the presence of CMV nuclear acids in the arterial walls of patients with atherosclerosis; they suggested that the human arterial wall may be a site of latency for this

virus and that CMV might play a role in the pathogenesis of atherosclerosis. Moreover, some authors have also implicated CMV infection in the production of vasculitis with pathologic involvement of both small and large veins. Thus, CMV infection has been linked to portal vein thrombosis.[20] Likewise, Muldoon et al[21] associated it to colic vein thrombosis. In view of all the above-mentioned aspects, it now seems clear that CMV infection could play a role in the pathogenesis of certain thromboses.

In our patient, CMV antigen assay became positive by day 15 after surgery and remained positive thereafter. A failed attempt to obtain negative readings was made 3 months after surgery, when the patient was treated with prophylactic intravenous ganciclovir sodium for 3 weeks. He subsequently received oral ganciclovir. Nevertheless, CMV retinitis developed in his right eye. The patient presented to us for evaluation of diminished vision in the left eye, in which we detected the CRVO, and CMV retinitis in the right eye was a casual finding. Therefore, we believe that the CRVO was posterior to CMV retinitis and that CMV infection may have triggered the occurrence of CRVO.

To summarize, factors related to surgical procedure (cardiopulmonary bypass) and immunosuppressive therapy (OKT3 and cyclosporine) might have played a role in the pathogenesis of CRVO in our patient. However, the fact that CRVO is infrequent after heart transplantation, and the concurrence with active CMV retinitis, leads us to believe that CMV infection may have played a major role in the pathogenesis of the CRVO. The presence of positive CMV antigen tests in heart transplant recipients should alert the ophthalmologist and attending physicians to the possibility of this development, and specific attempts to prevent these results should be made.

References

1. Porter R, Crombie AL, Gardner PS, Udall RP. Incidence of ocular complications in patients undergoing renal transplantation. *Br Med J.* 1972;3:133–166.
2. Rubin RH, Cosimi B, Tolkoff-Rubin NE, et al. Infectious disease syndromes attributable to cytomegalovirus and their significance among renal transplant recipients. *Transplantation.* 1977;24:458–464.
3. Pollard RB. Cytomegalovirus infections in renal, heart, heart-lung and liver transplantation. *Pediatr Infect Dis J.* 1988;7:S97–S102.
4. Cortina P, Díaz M, España E, et al. Acute frosted retinal periphlebitis associated with cytomegalovirus retinitis in a heart transplant patient. *Retina.* 1994;14:463–464.
5. Erice A, Jordan MC, Chace BA, et al. Ganciclovir treatment of cytomegalovirus disease in transplant recipients and other immunocompromised hosts. *JAMA.* 1987;257:3082–3087.
6. Keller JC, Linn JE. Central retinal vein occlusion in a heart trasplant patient: a case report. *J Tenn Med Assoc.* 1990;83:347.
7. Quinlan MF, Salmon JF. Ophthalmic complications after heart transplantation. *J Heart Lung Transplant.* 1993;12:252–255.
8. Klaver CCW, Hoyng CB, de Jong PTVM. Pigmentary irregularities and optic disc edema after heart transplantation. *Arch Ophthalmol.* 1995;113:1281–1285.
9. Chou S. Acquisition of donor strains of cytomegalovirus by renal transplant recipients. *N Engl J Med.* 1986;314:1418–1423.
10. Schooley RT, Hirsch MS, Colvin RB, et al. Association of herpesvirus infections with T-lymphocyte-subset alterations, glomerulopathy, and opportunistic infections after renal transplantation. *N Engl J Med.* 1983;308:307–313.
11. Rasmussen L, Kelsall D, Nelson R, et al. Virus-specific IgG and IgM antibodies in normal and immunocompromised subjects infected with cytomegalovirus. *J Infect Dis.* 1982;145:191–199.
12. Gutman FA. Evaluation of a patient with central retinal vein occlusion. *Ophthalmology.* 1983;90:481–483.
13. Allison RW, Limstrom SA, Sethi GK, Copeland JG. Central retinal vein occlusion after heart-lung transplantation. *Ann Ophthalmol.* 1993;25:58–63.
14. Solis RT, Kennedy PS, Beall AC Jr, et al. Cardiopulmonary bypass: microembolization and platelet aggregation. *Circulation.* 1975;52: 103–108.
15. Bartosh SM, Aronson AJ, Swanson-Pewitt EE, Thistlethwaite JR Jr. OKT3 induction in pediatric renal transplantation. *Pediatr Nephrol.* 1993;7:45–49.
16. Myers BD, Newton L, Boshkos C, et al. Chronic injury of human renal microvessels with low-dose cyclosporine therapy. *Transplantation.* 1988;46:694–703.
17. Ho DD, Rota TR, Andrews CA, Hirsch MS. Replication of human cytomegalovirus in endothelial cells. *J Infect Dis.* 1984;150:956–957.
18. Bruggeman CA, Debie WHM, Muller AD, et al. Cytomegalovirus alters the von Willebrand factor content in human endothelial cells. *Thromb Haemost.* 1988;59:264–268.
19. Hendrix MGR, Salimans MMM, van Boven CPA, Bruggeman CA. High prevalence of latently present cytomegalovirus in arterial walls of patients suffering from grade III atherosclerosis. *Am J Pathol.* 1990;136:23–28.
20. Arav-Boger R, Reif S, Bujanover Y. Portal vein thrombosis caused by protein C and protein S deficiency associated with cytomegalovirus infection. *J Pediatr.* 1995;126:586–588.
21. Muldoon J, O'Riordan K, Rao S, Abecassis M. Ischemic colitis secondary to venous thrombosis: a rare presentation of cytomegalovirus vasculitis following renal transplantation. *Transplantation.* 1996;61:1651–1653.