



Cytomegalovirus Infections in Cardiac Transplant Patients: An Experience at a Clinical Hospital, University of Chile

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ABSTRACT

Background. Since cytomegalovirus (CMV) infects between 20% and 50% of heart transplant patients, we reviewed our experience in 7 cases of this infection.

Methods. A prospective analysis of CMV infection was performed in heart transplant patients who received cyclosporine, azathioprine, or mycophenolate mofetil, and prednisone. An elevated creatinine de novo was managed with antibody induction.

Results. Between August 2001 and December 2005, we performed 22 heart transplants and 1 heart plus kidney transplant. Twenty-two patients were positive for CMV before transplantation. One patient died early because of graft failure. Immunosuppression included cyclosporine and prednisone (100%), azathioprine (52%), or mycophenolate (47%). Two recipients were induced with thymoglobulin and 13 with Daclizumab, while 8 did not receive any antibody. Nineteen patients received prophylaxis for CMV. Seven patients (30%) showed CMV infection, 6 of whom had received prophylaxis. Symptoms started at an average of 107 days posttransplantation in patients with prophylaxis. Three patients had gastritis, 2 pneumonia, and 1 colitis. One patient had concomitant lung aspergillosis. The two patients who received ATG developed CMV infections; 3 of the 12 with Daclizumab; and 2 who did not receive antibody. Of the CMV-infected subjects, 5 were on azathioprine and 2 on mycophenolate. All patients were treated with gancyclovir. The 1 patient with concomitant aspergillosis died.

Conclusions. The incidence of infection by CMV was 30%. Prophylaxis seemed to delay infection. Daclizumab induction did not increase the risk for CMV.

CYTOMEGALOVIRUS (CMV) infection is a frequent complication in cardiac transplantation, affecting 20% to 50% of cases.^{1,2} CMV presents as a primary infection, as reactivation of a previous infection, or as a superinfection. There are various risk factors that influence reactivation of CMV: serologic mismatching between donor and recipient; use of antibodies and other immunosuppressants; stress and other concomitant infections. Various organs can be affected, which accounts for the variable clinical presentation.¹⁻⁵ Herein we reviewed our experience, in 7 CMV cases among heart transplant recipients.

PATIENTS AND METHODS

This prospective analysis included adult patients transplanted from August 2001 to December 2005, all of whom had CMV serology in the pretransplantation evaluation. After transplantation, CMV antigenemia pp65 was performed regularly as well as at any time the disease was suspected. The immunosuppressive protocol in-

cluded cyclosporine (CsA), azathioprine, or mycophenolate mofetil, and prednisone. Thymoglobulin induction was used until December 2001, when Daclizumab was available to be used to delay the beginning of CsA because of abnormal renal function. The patients received prophylaxis against CMV, except when contraindicated. Patients were routinely instructed to consult the doctor because of suspected infections or unspecific symptoms.

RESULTS

Between August 2001 and December 2005, there were 23 transplants in our center: 22 heart grafts and 1 heart plus

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kidney transplant. Nineteen (82%) patients were men and 4 (18%) women. The average age was 38 years (range, 15–62 years). The etiologies were idiopathic cardiomyopathy (n = 16), coronary cardiopathy (n = 4), congenital disease (n = 1), or valvular in (n = 2). Twenty-two patients were seropositive for CMV before transplantation, and only 1 was seronegative. We did not have any information about the CMV serology of the donors.

A female patient died 48 hours after being transplanted because of a primary graft failure, so she was excluded from analysis. The immunosuppressive protocol included: CsA and prednisone in 100% of recipients, as well as azathioprine in 52% and mycophenolate mofetil (MMF) in 47%. Two patients received induction with ATG and 13. Daclizumab, while 7 did not receive any antibody induction.

Nineteen patients received CMV prophylaxis with gancyclovir (5 mg/kg) intravenously daily for 7 to 14 days; 7 of them continued with oral gancyclovir to complete 28 days. The others continued oral prophylaxis with Acyclovir (2400 mg/d) until 3 months. The seronegative patient received prophylaxis with valgancyclovir for 3 months and Acyclovir for another 3 months. Patients were examined serially for pp65 antigenemia. In the immediate posttransplantation period, all patients received prophylaxis for: *P. jiroveci* and *T. gondii* with cotrimoxazol and for tuberculosis with isoniazid during the first year, fluconazole (100 mg) for 30 days, and surgical prophylaxis until the withdrawal of drains.

RESULTS

Seven patients (31.8%) developed CMV infections; 6 recipients who received prophylaxis had symptoms starting at an average of 107 days posttransplantation (SD \pm 48), while the 1 patient who did not receive prophylaxis developed CMV symptoms earlier (at 35 days). Two patients who received ATG developed the infection, compared with 3 of the 12 recipients with Daclizumab and 2 patients who did not get any induction therapy. The five patients (45.5%) who took azathioprine, including 2 who also received ATG, displayed CMV infections. Two (18.2%) patients who received mycophenolate developed CMV. A patient presented an infection after an acute rejection episode, which required intravenous steroids. Two patients developed stomach pain after 190 and 54 days posttransplantation. The endoscopy showed gastritis. One of the patients had pp65 antigenemia with 29 nuclei; the other was negative. Both patients had a positive shell vial in a gastric biopsy. A third patient presented with stomach pain and 2 days thereafter had jaundice with elevation of transaminases, negative antigenemia, and a gastric positive shell vial. Another patient had diarrhea that developed into toxic megacolon which required colectomy. The biopsy showed the presence of CMV, with 2 previously negative samples for antigenemia and 2 negative shell vials.

Two patients presented with cough and dyspnea with radiography suggesting pneumonia. The first one presented at 102 days posttransplantation. He had positive antigenemia. The second patient had a heart plus kidney transplant and did not receive antiviral prophylaxis because of initial impaired kidney function. His symptoms began at 35 days posttransplantation, with positive antigenemia and a positive shell vial obtained from a bronchoalveolar lavage. The last patient had positive antigenemia with 9 nuclei, concomitant with pulmonary aspergillosis at 85 days posttransplantation.

All patients presented between 6 and 48 hours after the beginning of symptoms and receiving treatment with gancyclovir (10 mg/kg) IV for 7 to 28 days and followed by 1 or 2 months more with oral gancyclovir or valgancyclovir, with negative CMV results in the diagnostic technique used in each case. The treatment began an average of 24 hours from admission. Six patients improved; the patient with aspergillosis died.

DISCUSSION

The incidence of CMV infection among our group was 30%, a rate similar to that reported in the literature for cardiac transplantation.^{1,2} The use of prophylaxis may have retarded reactivation of CMV,⁶ to an average of 105 days posttransplantation, when immunosuppression was reduced and there was a better response to treatment. In our group of patients, the 2 who received thymoglobulin developed infections, but not the patients who received induction with Daclizumab. The latter cohort did not show a greater risk for CMV compared with no induction. The greater frequency of infection among patients who received azathioprine may be explained because 2 of these 5 received thymoglobulin.

As has been previously described, acute rejection episodes and serious infections promote virus reactivation,^{1,2} as observed in our patients, because one presented with infection after an acute allograft rejection episode and another in relation to systemic aspergillosis.

The gastrointestinal system was the most frequently affected; gastritis being the most frequent presentation. In this group of patients, pp65 antigenemia showed low sensitivity (33%), with shell vial the diagnostic method in the 3 cases of gastritis. In the case of the patient with colitis, both methods were negative and only the histological study yielded the diagnosis.

In conclusion, CMV infection is frequent among heart transplant patient, with many forms of clinical presentation that require a high degree of clinical suspicion and the use of more than one diagnostic method. Our results were comparable to those described in the literature.

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