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Influence of cytomegalovirus infection in the development of cardiac allograft vasculopathy after heart transplantation

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cardiac allograft vasculopathy;
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calcium channel blocker;
cardiac angiography

BACKGROUND: Cardiac allograft vasculopathy (CAV) is a major cause of long-term morbidity and mortality after heart transplantation (HTx), whose relationship with CMV infection is uncertain. This study evaluated the influence of CMV infection in the development of CAV.

METHODS: We enrolled 166 consecutive HTx recipients who underwent their first transplant from January 1995 to July 2002. All patients received 14 days of intravenous ganciclovir and were prospectively monitored for CMV infection during the first year after HTx. CAV was diagnosed by coronary angiography performed at 1, 5, and 10 years after HTx, following the new criteria of the International Society for Heart and Lung Transplantation. We collected all variables potentially related with the development of CAV. Risk factors were studied using a complementary log-log model.

RESULTS: After a median follow-up of 11 years (range, 1–17 years), 72 patients (43%) developed CAV (63.8% CAV_1, 15.2% CAV_2, 20.8% CAV_3). Symptoms secondary to CAV were present in 32% of these patients, and 8% died because of it. In the regression multivariate analysis, independent variables associated with the development of CAV were donor age (hazard ratio [HR], 1.028; 95% confidence interval [CI], 1.002–1.053; $p < 0.028$), presence of cellular acute rejection $\geq$ 2R (HR, 1.764; 95% CI, 1.011–3.078; $p < 0.0414$), CMV infection (HR, 2.334; 95% CI, 1.043–5.225; $p < 0.0354$), and not having been treated with a calcium channel blocker (HR, 0.472; 95% CI, 0.275–0.811; $p < 0.0055$).

CONCLUSIONS: Standardized angiographic criteria show CMV infection is associated with the development of CAV.

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Cardiac allograft vasculopathy (CAV) remains the Achilles heel of heart transplantation (HTx). Current prevalence of CAV among HTx patients is 20% at 3 years, 30% at 5 years, and 45% at 8 years after HTx.[1] According to the International Society for Heart and Lung Transplantation (ISHLT) Registry, CAV is one of the most important causes of death after HTx, accounting for 10% to 13% of deaths occurring more than 1 year after HTx and may be present in patients who die after the first year due to "graft failure" (16% to 27%).[1]

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CAV is a long-term complication of HTx, but most studies of the pathogenesis of CAV are hampered by a very short follow-up and the lack of uniform criteria in its definition. CAV is detected mainly by coronary angiography,[2] which is the best screening tool to detect the presence of CAV. However, the different angiographic definitions used make it impossible to draw solid conclusions regarding the influence of a specific factor in the development of CAV. The recently published standardized nomenclature for CAV by the ISHLT will be an important step forward to allow a better comparability between studies[3] and a useful tool for prognostic stratification after HTx.[4]

Several factors have been linked with the development of CAV, including donor and recipient characteristics and post-HTx complications.[1] In particular, cytomegalovirus (CMV) infection has been occasionally linked with CAV as a part of the so-called indirect effects in HTx recipients.[5] However, a recent meta-analysis of risk factors associated with the development of CAV did not find a conclusive association between CMV infection and CAV.[6] Thus, the main objective of our study was to evaluate the influence of CMV infection and other risk factors for the development of CAV.

Methods

The Local Ethical Committee approved this investigation.

Study design

A single-center, retrospective, observational study from prospectively collected data was designed to evaluate the relationship between CMV infection and CAV. We conducted this study by following the recommendations for observational studies of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[7]

Study population

Consecutive patients who received their first HTx from January 1995 to July 2002 and survived at least 1 year were included in the study. Patients were excluded when they underwent repeat HTx, had an inadequate CMV sampling (<90% of the protocolized samples), or did not have an adequate coronary angiographic study. Follow-up continued until death, retransplantation, or until follow-up ended in December 31, 2011.

Immunosuppressive therapy

Induction immunosuppressive therapy included OKT3 (5 mg/day for 14 days) or, after June 2002, 2 doses of basiliximab (20 mg) on Days 1 and 4 after surgery. Methylprednisolone was administered at 500 mg intravenously before surgery and at 125 mg intravenously every 8 hours for 3 doses after the operation, followed by prednisone at 1 mg/kg/day orally, tapered by 0.1 mg/kg on alternate days to 0.2 mg/kg/day and reduced to 0.1 mg/kg/day after 1 year. Azathioprine was administered at 2 mg/kg/day orally. After January 2002, azathioprine was substituted by mycophenolate mofetil (2–3 g/day). As a calcineurin inhibitor we used cyclosporine A (5 to 8 mg/kg/day) to maintain serum cyclosporine A levels within the range of 250 to 350 ng/ml during the first year and from 100 to 200 ng/ml for the second year and all following.

CMV diagnosis and CMV-related definitions

Fourteen CMV anti-genemias were collected during the first 6 months after HTx (Monofluo kit CMV, BioRad, Marnes-la Coquette, France). It was measured in number of total leukocytes pp65 positive/200,000 leukocytes).

CMV infection was defined as evidence of CMV replication regardless of symptoms, upon the sole presence of a positive anti-genemia test. CMV disease was defined as evidence of CMV infection with attributable symptoms. CMV disease can be further categorized as a viral syndrome with fever, malaise, leukopenia, and thrombocytopenia or as a tissue-invasive disease.[8,9]

Asymptomatic viremia was diagnosed when a positive anti-genemia test was not accompanied by any clinical symptom. Patients with asymptomatic viremia were compared only with patients without CMV infection, and therefore, patients with CMV disease were excluded from this analysis.

We defined a "high CMV viremia" if 3 or more consecutive or non-consecutive anti-genemia tests showed more than 10 cells/200,000 leukocytes.

Antiviral therapy

All patients, irrespective of their CMV serostatus, received universal CMV prophylaxis with intravenous ganciclovir (5 mg/kg/day) during the first 14 days after HTx as the only anti-CMV prophylactic therapy. Preemptive therapy was not performed during the follow-up, but patients with asymptomatic viremia were monitored closely for signs and symptoms of CMV disease, and when present, intravenous ganciclovir treatment for 14 to 21 days was administered.

Coronary angiographic studies

CAV diagnosis was done through a retrospective review of all coronary angiographic and echocardiographic studies performed in every patient by protocol at 1, 5 and 10 years after HTx, following standardized ISHLT nomenclature.[3] Coronary angiography was performed using standard techniques after pre-treatment with nitroglycerine. Two expert cardiologists, blinded to the clinical course of patients, examined all angiograms. We defined the presence of CAV as a status $\geq CAV_1$.

Risk factor analysis

Risk factor data were collected by a retrospective review. More than 100 variables were collected as potential risk factors for CAV, including recipient and donor characteristics, immunosuppression, specific treatments, and complications (acute rejection episodes, severe infections different than CMV, and malignancies).

We defined severe infections other than CMV as all bacterial, viral, and fungal infections that needed hospitalization or intravenous anti-biotic treatment and also infections caused by varicella-zoster virus.

In addition, we collected classical cardiovascular risk factors before HTx and at 1, 5 and 10 years after HTx, including diabetes, hypertension, smoking status, hypercholesterolemia (defined as cholesterol > 220 mg/dl) and hypertriglyceridemia (triglyceride