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Petri K. Koskinen
Karl B. Lemström
Markku S. Nieminen
Pekka J. Häyry
Irmeli T. Lautenschlager

Vascular cell adhesion molecule-1 (VCAM-1) is induced during cytomegalovirus infection in vascular structures of heart allografts

P. K. Koskinen (✉) · K. B. Lemström
M. S. Nieminen · P. J. Häyry
I. T. Lautenschlager
Transplantation Laboratory,
University of Helsinki, POP 21,
SF-00014 Helsinki, Finland

Abstract This study was designed to investigate the expression of vascular cell adhesion molecule-1 (VCAM-1) and the counter-ligand VLA-4 (CD 49d) in frozen sections of endomyocardial biopsies (EMBs) of heart allografts in relation to the onset of cytomegalovirus (CMV) infection diagnosed by CMV antigenemia. Altogether, 105 EMBs were obtained from 21 heart transplant recipients. Serial EMBs from nine patients with CMV infection, from five patients with rejection, and from seven patients with a noncomplicated postoperative course were analyzed. Associated with CMV infection, capillary expression of VCAM-1 was significantly induced when compared to control biopsies ($P < 0.0001$). A striking difference in the expression of VCAM-1 during rejection and CMV infection was observed: in most rejecting biopsies only a few capillaries stained faintly for VCAM-1, whereas during CMV infection, multifocal intense staining was found ($P < 0.0001$).

Key words Heart transplantation
CMV infection · VCAM-1

Introduction

Previous studies have shown that during acute heart allograft rejection the expression of vascular adhesion molecules (VCAM) is induced [4]. Together with MHC molecules, adhesion molecules have an important role in T cell activation [1]. This study describes the impact of cytomegalovirus (CMV) infection on the expression of VCAM-1/VLA-4 ligand pair in the endomyocardial biopsies (EMBs) of human heart allografts.

Patients and methods

Patients

Serial EMBs from nine patients with CMV infection, from five patients with rejection, and from seven patients with a noncomplicated postoperative course (controls) were analyzed Patients with both CMV infection and acute rejection were excluded. Rejection episodes were diagnosed and graded according to the ISHT [2]. The basic immunosuppression consisted of cyclosporin A, methylprednisolone (MP), and azathioprine. Rejections were treated either with high-dose MP alone or combined with ATG. CMV hyperimmuneglobulin prophylaxis was given preoperatively for CMV seronegative patients. Also, all recipients received aciclovir prophylaxis against herpes virus infections for the first 3 months. In case of a severe symptomatic CMV infection, ganciclovir, CMV hyperimmuneglobulin, or both were administered.

Demonstration of CMV antigenemia, VCAM-1 and VLA-4

A monoclonal antibody (mAb) against CMC-specific antigens (pp65) (Biotest Pharma, Clonab, Frankfurt, Germany), mAbs to VCAM-1 (British Biotechnology Products, Oxon, UK) and to VLA-4 (Immunotech SA) were applied. A peroxidase-conjugated rabbit anti-mouse Ab (Dako, Copenhagen, Denmark) and goat anti-rabbit Ab (Tago Inc., Burlingame, Calif.) were used as second and third Abs, and the reaction was revealed by AEC (3-amino-9 ethyl carbatzole) solution containing hydrogen peroxide. Mayer's

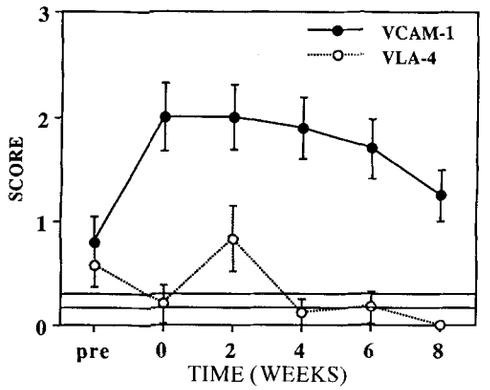

Fig. 1 Induction and expression of VCAM-1 and VLA-4 during CMV infection. *Bars* indicate SEM, *box* indicates mean ± SEM values of controls

hemalun was used for counterstaining. The scoring of staining was from 0 to 3.

Statistics

Data were analyzed using the Mann-Whitney *U* test.

Results

A clear induction of VCAM-1 occurred in relation to the onset of CMV infection (Fig. 1). Associated with CMV infection, capillary expression of VCAM-1 was significantly induced when compared to control biopsies ($P < 0.0001$). A striking difference in the expression of VCAM-1 during rejection and CMV infection was observed: in most rejecting biopsies only a few capillaries stained faintly for VCAM-1, whereas during CMV infection, multifocal intense staining was found ($P < 0.0001$). The number of VLA-4-positive leukocytes was higher during rejection compared with CMV infection (nonsignificant). However, a short-term induction of VLA-4 occurred after the onset of CMV infection (nonsignificant; Fig. 1).

Discussion

The VCAM-1/VLA-4 ligand pair may play an important role in adhesion of lymphocytes and monocytes to capillary endothelium during active CMV infection and, hence, contribute to the pathogenesis of subendothelial lymphocytosis that we have reported in small intramyocardial vessels of heart allografts during CMV infection [3]. These CMV-related findings of the vascular wall may offer insight into the pathogenesis of increased vasculopathic changes reported in CMV-infected heart transplant recipients.

References

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