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Expression of the cytomegalovirus genome in kidney allografts during active and latent infection

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Abstract Cytomegalovirus (CMV) infection is suggested to be a risk factor for chronic rejection. Here we investigated whether CMV can persist in renal allografts, and in which structures the viral genome is found during an acute infection and a latent period after an active infection. CMV infection was diagnosed in 72/157 patients by CMV antigenemia tests and by viral cultures. CMV antigens were demonstrated in 38 available biopsies by immunohistochemistry, and CMV genome by DNA hybridization in situ. Standard histology was also performed. CMV antigens were detected in 7/15 biopsies obtained during acute infection, in three with acute rejection, and chronic changes in the other biopsies. CMV genome was located in inflammatory cells, in tubuli and in the capillary endothelium. During a latent period without a positive finding in blood or urine, CMV antigens were still found in 6/31 biopsies. CMV DNA was found in inflammatory cells, tubular and glomerular structures and in the endothelium of the arterioles. During the latent period with persistent CMV in the graft, in most cases (10/12) mild to moderate chronic changes were recorded.

Key words Cytomegalovirus · Chronic rejection · Renal transplantation

Introduction

In addition to the clinical symptoms, cytomegalovirus (CMV) may cause renal transplant glomerulopathy [10] and is suggested to be involved in the mechanisms of allograft rejection [8, 9, 13]. Chronic rejection is a major problem in transplantation, and CMV infection is thought to be one of several risk factors for chronic rejection [4]. In kidney transplantation, the role of CMV in chronic rejection has been demonstrated in experiemental animal models [7, 14], but there is no published clear-cut clinical study to prove the suggestion that CMV causes or enhances the characteristic histopathological changes of chronic renal allograft rejection.

Human kidney cells of glomerular, tubular and vascular origin can all be infected by CMV [11]. In this study, we investigated whether CMV can persist in renal allografts, and in which structures the viral genome is found during an acute infection with positive findings from blood and urine, and during a latent period after an active infection.

Patients and methods

In a renal transplant patient population of 157 patients treated at the Department of Nephrology, Helsinki University Central Hospital, CMV infection was diagnosed in 72 patients (median 55 days) after transplantation. The diagnosis of CMV infection was based on direct immunodetection of viral antigens in peripheral blood leukocytes [12] by using immunoperoxidase staining and a monoclonal antibody against CMV pp65-antigens, and/or on viral cultures from blood and urine.

A total of 46 renal biopsies were available from 38 of the 72 patients with CMV infection. CMV was also demonstrated in frozen sections of the biopsies by pp65 antigen detection, using immunoperoxidase staining. Biopsies were further characterized by CMV-

DNA hybridization in situ, using a biotinylated probe [2]. Standards histological evaluation of the biopsies was also performed in parallel.

Results

Acute CMV infection

CMV-specific antigens were detected in seven out of 15 biopsies obtained during acute CMV infection. The viral antigens were located mainly in the inflammatory cells but also in some capillary endothelial cells. By DNA hybridization in situ, CMV genome expression was located in the inflammatory cells, as well as in the tubulus epithelium, and in one biopsy in the capillarary endothelium.

In biopsy histology, acute rejection was found in three cases with positive CMV finding. In the other biopsies chronic changes including tubular atrophy, interstitial inflammation and fibrosis, thickening of the vascular walls of the arteries were seen in various degrees.

Latent CMV infection

During a latent period after positive findings in blood or in urine, CMV antigens were still found in six biopsies of 31 (median 119 days after the last positive finding). Antigens were located, in addition to the inflammatory cells, in a few tubular epithelial cells and capillary endothelial cells. DNA hybridization in situ demonstrated a strong CMV genome expression which was located in several tubuli and some glomerular structures and in two cases in the endothelium of the arterioles.

The histology of one biopsy was almost normal with mild fibrosis and few inflammatory cells. Mild acute rejection was found in one case. In other biopsies, mild to moderate chronic changes with increased glomerular matrix tubular atrophy, and interstitial fibrosis and inflammation were seen.

Discussion

CMV could be found in the inflammatory cells as well as in the tubular and capillary structures concurrently with active excretion of the virus. In some cases, persistent expression of CMV antigens and genome could still be found in various tubular, glomerular and vascular structures of the graft during the latent period several weeks even months after an active infection. Persistent CMV in the graft was associated with mild acute or chronic rejection changes in the biopsy histology.

The involvement of CMV in chronic vasculopathy in heart transplantation is evident [3, 5], and persistent CMV has been found in liver allografts with vanishing bile duct syndrome, known as chronic rejection of hepatic allografts [1, 6]. In a kidney transplant rat model of chronic rejection, CMV has been found to increase endothelial proliferation of small vessels, intimal proliferation of small and large arteries, persistent interstitial inflammation, glomerular sclerosis, tubular atrophy and fibrosis [7]. These are the typical histopathological changes of chronic rejection of kidney allografts. In this animal model, CMV has been shown to prolong and increase graft inflammation and accelerate chronic rejection. In another rat model, CMV infection was associated with an increased acute rejection rate and enhanced chronic allograft changes [14].

In clinical transplantation, it is difficult to prove that CMV may enhance the development of chronic changes, while the etiology of chronic rejection is multifactorial with direct and indirect immunological and non-immunological factors involved in the long-term course of several years. However, our study demonstrates that the CMV genome may persist in the renal allograft for a long period, and this persistence is usually associated with the development of chronic changes in the graft.

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