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Prospective study of pulmonary function for cyclomegalovirus infection after renal transplantation

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Abstract Pulmonary involvement remains the main complication of cytomegalovirus (CMV) infection in renal transplantation (RT). Early diagnosis is required for the best management of patients, and preemptive therapy could be a successful approach. In order to define the predictive value of lung alveolocapillary abnormalities. We prospectively studied 26 renal transplant recipients for their diffusing capacity of carbon monoxide (DLCO) and their pulmonary clearance of a ^{99m}Tc-DTPA aerosol. Patients were studied before transplantation and then every 2 weeks up to the end of the 3rd month following RT. Viral blood cultures and serological determinations were performed every week during these first 3 months. Bronchoalveolar lavage (BAL) was done in case of CMV disease. Statistic analysis was done using Student's *t*-test and Pearson's chi-square test. During the 3-month follow-up, 13 patients remained free of CMV infection. Three non-infected and 8 infected patients showed DTPA clearance abnormalities ($P < 0.05$). Six non-infected and 7 infected patients showed DLCO disturbance ($P > 0.50$). DTPA clearance were significantly modified on days 45 and 60 in the infected group. Serial DTPA scanning, in association with viral blood cultures, could be a useful test to avoid unnecessary BAL in a preemptive therapy strategy.

Key words Renal transplantation
Cytomegalovirus

Introduction

Cytomegalovirus (CMV) infection is the most frequent infectious complication observed in renal transplant recipients and may be symptomatic in more than 30% of the patients [1]. Pneumonitis remains the main cause of morbidity and mortality associated with CMV infection. Traditionally, antiviral therapy has been administered either prophylactically or therapeutically. Recently, Schmidt et al. [2] described an attractive new approach called preemptive therapy. In this study, early detection of CMV pulmonary infection, followed by treatment of asymptomatic infection with ganciclovir, has been shown to prevent CMV pneumonia in most recipients. The cornerstone of the success of this method is the need for a reliable laboratory test to identify patients at risk. The diagnosis of subclinical pulmonary CMV infection is often difficult to asses in renal transplant recipients even when bronchoalveolar lavage is performed. Because of the crucial need to find a predictive test, we have prospectively evaluated the benefits of functional respiratory measurements in the early dignosis of CMV pneumonitis in renal transplant recipients.

Patients and methods

Thirty-four consecutive renal transplant candidates were evaluated for pulmonary function by studying the diffusion capacity of carbon monoxide (DLCO) and ^{99m}Tc-DTPA aerosol clearance. Eight patients were excluded from the study because of pretransplant DLCO abnormalities. The remaining 26 patients received a cadaver renal allograft. Serial measurements of DLCO and DTPA clearance were both performed on days 15, 30, 45, 60 and 90 following transplantation.

^{99m}Tc-DTPA aerosol scanning was performed according to the method described by Rosso et al. [3]. The pulmonary ^{99m}Tc-DTPA clearance rate was calculated from the negative slope of the regression line and expressed in terms of the percentage of decrease in radioactivity per minute (%.mn^{-1}). A clearance rate was considered increased if it was higher than two standard deviations from the mean value of the normal non-smoking subject in the laboratory (1.1 ± 0.34 % min^{-1}).

DLCO was measured by a standard technique usually performed in our pulmonary explorations laboratory. The results were corrected according to the hemoglobin concentration of the patients.

Bronchoalveolar lavage was performed in case of CMV disease. Viral blood cultures and serological determinations were performed every week during the first 3 monts. CMV infection was defined as CMV isolation from peripheral blood or as a four-fold or greater rise in antibodies (IgG and IgM), or CMV detection (culture, immunofluorescence, cytopathic effect) in bronchoalveolar lavage. CMV disease was defined by the association or relevant clinical signs and evidence of CMV infection.

Quantitative data were compared between and within both groups (CMV infected vs CMV non-infected) by an unpaired Student's *t*-test. Qualitative data were compared by the chi-square test.

Results

During the 3 month follow-up, 13 patients remained free CMV infection, 13 patients were infected and CMV disease was observed in 8 patients. The results of DLCO studies and DTPA clearances are shown in Table 1. Despite any evidence of fluid overload or sepsis, 6 of the 13 non-CMV infected patients showed reduced DLCO, and 3 of them had an accelerated DTPA clearance. These tests were both disturbed in only 1 patient. Of the 13 patients with CMV infection, 7 had decreased DLCO and DTPA clearance was accelerated in 8 patients. The incidence of accelerated DTPA clearance was significantly increased in the group of CMV infected patients ($P < 0.05$). This test had a positive predictive value of 72.7% and a negative predictive value of 37.5%.

Table 1 DLCO and pulmonary DTPA clearance

	CMV+ patients	CMV− patients
Total	13	13
Decreased DLCO	7	6
Increased DTPA clearance	8*	3

* $P < 0.05$
Sensitivity = 61.5%
Specificity = 76.9%
Predictive positive value = 72,7%

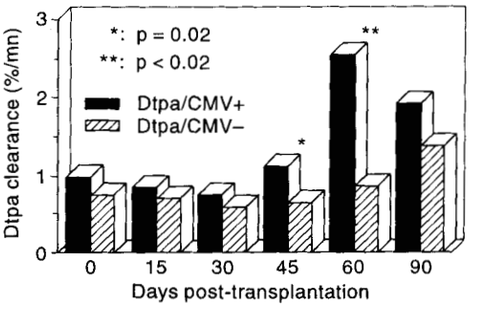

Fig. 1 ^{99m}Tc-DTPA clearance kinetics

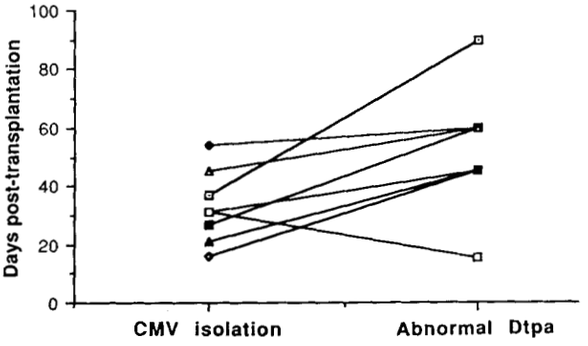

Fig. 2 Delay between CMV isolation and DTPA disturbance

CMV was isolated from the bronchoalveolar lavage fluid in 6 of the 8 patients with CMV disease. DLCO was reduced in only 1 patient and DTPA clearance was increased in 3 patients.

The kinetics of DTPA clearance values are shown in Fig. 1, and the delay in the diagnosis of CMV infection is shown in Fig. 2. DTPA clearance measurements are significantly increased around day 60, and in all patients but one, these abnormalities occurred after the diagnosis of CMV infection.

All the patients had a favorable course. Ganciclovir was administered for two weeks in patients with virological evidence of CMV in the bronchoalveolar lavage.

Discussion

The clinical spectrum of CMV infection in renal transplant recipients is very large, ranging from asympto-

matic infection to overwhelming disease, chiefly associated with interstitial pneumonia. This diversity explains in part the various therapeutic strategies presently used to control CMV infection in renal transplant recipients: intravenous ganciclovir, perhaps in conjunction with anticytomegalovirus hyperimmune globulin in the most serious cases, has been shown to be effective in treating active disease [4]. Both hyperimmune globulin [5] and high-dose oral acyclovir [6] have been shown to have significant efficacy in the prophylaxis of cytomegalovirus disease. Preemptive therapy with moderate-dose ganciclovir for the duration of the antilymphocyte antibody appears to hold great promise [7]. Similarly, in bone-marrow transplant recipients, preemptive treatment of patients with virus shedding has been reported to be effective in preventing the development of CMV interstitial pneumonia [2, 8].

Preemptive therapy seems the most attractive strategy, but this approach requires the identification of a reliable test to identify patients at risk. In renal transplant recipients, only a small proportion of viremic patients will develop pulmonary infection [9], and preemptive treatment in all the patients with positive surveillance cultures would unnecessarily expose many patients to ganciclovir. In the very interesting approach described by Schmidt et al. [2], preemptive therapy was initiated when the bronchoalveolar lavage fluid culture was positive for CMV. However, this aggressive diagnostic intervention was no more effective than blood screening and cannot be serially repeated [2, 8]. Moreover, isolation of CMV in the bronchoalveolar-lavage fluid can be observed without associated pneumonia [10].

In order to define a reliable marker for early pulmonary dysfunction in renal transplant recipients, we analyzed the modifications of lung alveolocapillary permeability using DLCO and ^{99m}Tc-DTPA aerosol clearance measurements. Both of these tests study the permeability characteristics of the lung parenchyma [3], and serial measurements can easily be performed.

In our study, decreased DLCO was frequently observed in CMV infected patients, as previoulsy reported [11], but the high rate of positivity in non-infected transplant recipients excludes the possibility of using this test as a reliable marker for subclinical pulmonary CMV infection. In these patients, DLCO abnormalities might be the consequences of immunological activation associated with the alloreaction. However, the possibility remains that this test could detect in situ reactivation of CMV.

DTPA scanning might be a more promising test for detecting subclinical CMV pneumonia. Increased DTPA clearance was observed in 8 of 13 CMV-positive compared to 3 of 13 CMV-negative patients. These abnormalities were observed after blood isolation of the virus, suggesting that this test could not be used for preemptive therapy. However, in renal transplant patients, preemptive therapy of CMV pulmonary infection must be not described by Rondeau et al. [12] for which curative therapy, if necessary, might be more relevant than preemptive therapy. Our current strategy is to investigate weekly the asymptomatic patients blood cultures and DTPA scanning. DTPA clearance, is abnormal bronchoalveolar lavage is performed to exclude any other infection and ganciclovir is administered.

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