CHAPTER 5

SUBCLINICAL PNEUMONITIS DURING CYTOMEGALOVIRUS INFECTION AFTER KIDNEY TRANSPLANTATION

E.F. de Maar, A.M. Kas-Deelen, Th.W. van der Mark, T.H. The, A.M. Tegzess, R.J. Ploeg, and W.J. van Son

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ABSTRACT

In addition to life-threatening pneumonia, cytomegalovirus (CMV) may also cause subclinical pulmonary dysfunction after kidney transplantation. To investigate the role of plugging of cytomegalic endothelial cells (CEC) in the pulmonary capillary bed we prospectively determined specific carbon monoxide diffusion capacity (KCOc), and its components: the pulmonary diffusing membrane factor (Dm) and pulmonary capillary blood volume (Vcap) before and during CMV infection in 13 kidney transplant recipients and 13 controls.

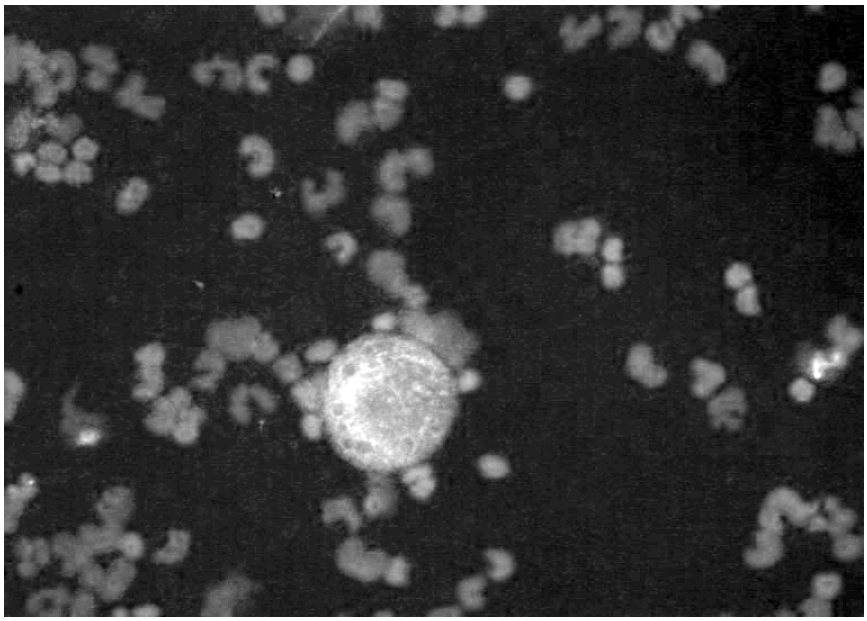
During CMV infection median KCOc decreased significantly due to a decrease in both Vcap and Dm. We illustrate the course of pulmonary diffusion in a male kidney transplant recipient with CMV infection.

We conclude that kidney transplant recipients with CMV infection have significant pulmonary diffusion disturbances due to a combination of lower Vcap and lower Dm. The most likely explanation for this phenomenon is a local inflammatory process due to CMV and not plugging of cytomegalic endothelial cells.

5.1 INTRODUCTION

Cytomegalovirus (CMV) infection is a frequent infectious complication after kidney transplantation. Despite the fact that in many kidney transplant recipients CMV infections occur a substantial part of these is asymptomatic. Most patients in whom a CMV infection causes symptoms have a self-limiting CMV syndrome that consists of fever with malaise and arthralgias, leucocytopenia, thrombocytopenia, and elevated serum liver enzymes (especially transaminases).

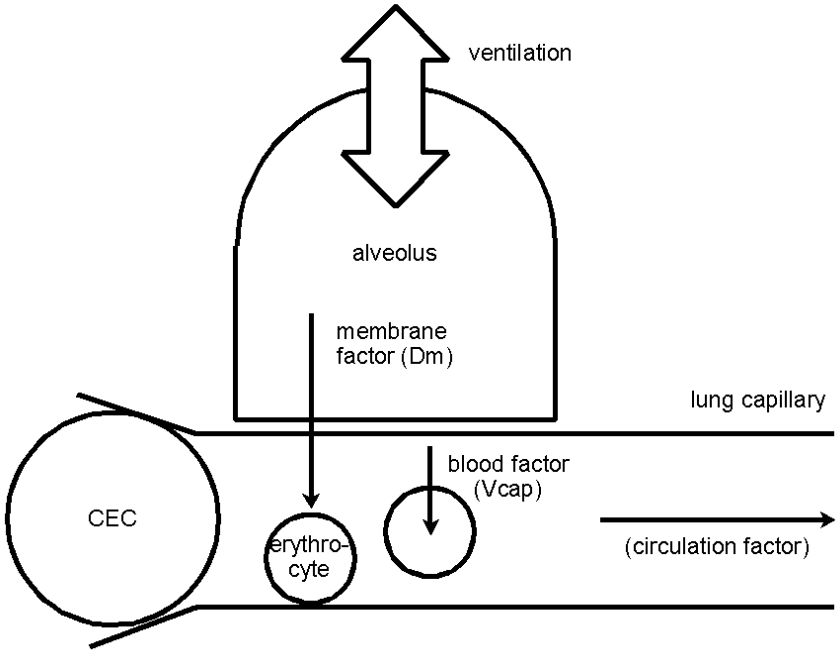
Figure 5.1 **This photo shows a cytospot of the mononuclear cell fraction (counterstained for DNA) from a kidney transplant recipient with cytomegalovirus infection. The large bright cytomegalic endothelial cell (CEC) in the center is positive for both CMV- and endothelial specific monoclonal antibodies.**



Pulmonary symptoms are less common; clinical manifestations of CMV-related pulmonary involvement range from mild dyspnea to severe respiratory insufficiency due to CMV pneumonitis. Subclinical pulmonary involvement has been found in almost all kidney transplant patients with CMV infection by measuring specific carbon monoxide diffusion capacity [1]. The reason for the fall in pulmonary diffusion during CMV infection remains speculative. Recently large CMV-infected endothelial cells (diameter 30-35 μm) in the peripheral blood of patients with an

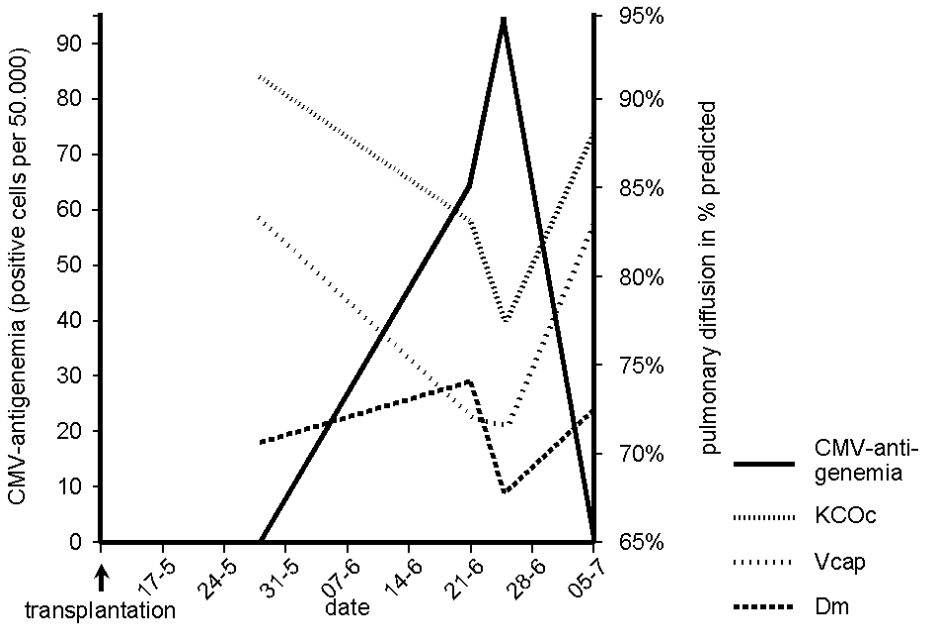
active CMV infection were described (figure 5.1) [2, 3]. Plugging of these large cytomegalic endothelial cells in the pulmonary capillary bed could decrease pulmonary capillary volume and this could probably explain the fall in CO diffusion (figure 5.2).

Figure 5.2 Plugging of large cytomegalic endothelial cells is not the only explanation for diminished pulmonary diffusion during CMV infection.



To investigate the role of plugging cytomegalic endothelial cells (CEC) in the pathogenesis of disturbed pulmonary diffusion during CMV infection we prospectively determined specific carbon monoxide diffusion capacity (KCOc) and its components: the pulmonary diffusing membrane factor (Dm) and pulmonary capillary blood volume (Vcap) before and during CMV infection in kidney transplant patients and in a control group. We demonstrate the course of pulmonary diffusion parameters in a male kidney transplant recipient with CMV infection (figure 5.3).

Figure 5.3 Course of CMV-antigenemia (left Y-axis) and KCOc, Dm and Vcap (right Y-axis) in a kidney transplant recipient with CMV infection.



5.2 METHODS

In 13 kidney transplant recipients with active CMV infection pulmonary function was measured before (median postoperative day 19) and during the infection (median postoperative day 56). None of these patients had a history of pulmonary disease and all had normal physical examination and chest X-ray. Initial immunosuppression consisted of cyclosporine and low-dose prednisolone. No CMV prophylaxis was given. The transfer factor (diffusing capacity, for Hb corrected) for carbon monoxide (TlCOc) and its components (figure 5.2), diffusing capacity of the alveolar-capillary membrane (Dm) and volume of blood in the pulmonary capillaries (Vcap) were determined from triplicate measurements of TlCO at high (88%) and low (19.2%) concentrations of inspired oxygen. The single breath technique of Krogh as modified by Ogilvie and Cotes was used [4]. Carbon monoxide was measured with an infrared spectrophotometer and helium with a thermal conductivity method (ML-Masterlab-Transfer; Jaeger, Germany). The specific diffusion capacity (KCOc) was calculated by dividing TlCOc by the alveolar volume [4]. The Dm and the Vcap were derived from the equation of Roughton and Forster [5]. Values were expressed as percentage

of those predicted, with the predicted values being taken from Quanjer and Cotes [6, 7]. Diagnosis of active CMV infection was confirmed using the CMV antigenemia assay, as described by Van der Bij et al. [8, 9] and reviewed by Chou [10] and by Ljungman and Griffiths [11].

5.3 RESULTS

During CMV infection in thirteen kidney transplant recipients median KCOc decreased significantly by 26% of the initial value (median KCOc 78 vs. 106; $P < 0.005$) due to a decrease in both Vcap (median Vcap compared to baseline 80 vs. 104; $P < 0.005$) and Dm (median Dm compared to baseline 68 vs. 95; $P < 0.01$). In controls without CMV median KCOc on postoperative day 56 decreased only by 12 % from baseline values (91 vs. 104; $P < 0.05$) due to a slightly lower Vcap (88 vs. 95; $P < 0.005$) but a similar Dm (87 vs. 83; NS). The decrease in KCOc and Vcap in controls was significantlysmaller than in recipients with CMV infection. None of the patients had pulmonary symptoms, six patients were asymptomatic, six patients had four out of five of the following symptoms: fever, malaise, leukocytopenia, thrombocytopenia and elevated liver enzymes, one patient had only elevated transaminases. Eight patients received antirejection treatment: four with pulse prednisolone followed by ATG and four with only pulse prednisolone. In Figure 5.3 the course of KCOc, Vcap and Dm in a 48-year-old male kidney transplant recipient is illustrated. This patient was transplanted May 10, 1996 after two years of dialysis. Before transplantation he had been CMV-seronegative and he was transplanted with a kidney from a seropositive donor. His immunosuppressive regimen consisted of cyclosporin and low dose prednisolone. He had no rejection episodes before or during CMV infection. During the CMV infection he developed no pulmonary symptoms and had a normal chest X-ray. He was treated with ganciclovir.

5.4 DISCUSSION

We conclude that kidney transplant recipients with CMV infection have a disturbed specific diffusion capacity for carbon monoxide caused by both, a decrease in capillary volume as well as a decrease in membrane factor. The course of KCOc, Vcap and Dm is demonstrated in a male transplant patient with CMV infection. CMV infected

cytomegalic endothelial cells (CEC, diameter 35 μm) [2, 3] cannot, at least theoretically, pass the pulmonary capillaries (diameter 5 μm). Plugging of these cytomegalic endothelial cells alone, however, is not an explanation for the decrease in diffusion as this should only affect Vcap and not Dm. We speculate that a local inflammatory process due to CMV causes interstitial edema and capillary obstruction. This would explain the decrease in both capillary volume and membrane factor. The CECs containing active replicating CMV [2, 3] might contribute to the decrease in KCOc by spreading infection in the lungs. This may then lead to a locally CMV induced inflammatory response. The difference between subclinical and overt pneumonitis is probably only quantitative. Determination of subclinical pneumonitis, however, allows us to recognize important pathophysiological clues. Also, subclinical pneumonitis could render the lungs more susceptible to opportunistic infections.

5.5 REFERENCES

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