INCIDENCE OF CYTOMEGALOVIRUS INFECTION AFTER KIDNEY TRANSPLANTATION

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Cytomegalovirus (CMV), one of the herpes group of viruses, is a common human pathogen (Stern and Elek, 1965). Most infections in adults are subclinical, but clinically evident infection has been described in healthy adults (Klemola et al., 1967; Carlström et al., 1968). Recent studies have shown that CMV infection is particularly frequent in renal allograft recipients (Rifkind et al., 1967; Craighead et al., 1967).

In November 1966, we began a comprehensive study of the incidence and clinical significance of CMV infection among the renal allograft recipients in the Aarhus series. It was possible to carry out longitudinal virological and serological studies in 21 patients for a minimum of seven months after transplantation. Retrospective serological studies were done in 13 patients. In addition, a histological study of autopsy material from 17 patients was also undertaken.

A more complete description of the patient material as well as of the methods used will be published elsewhere (Andersen and Spencer, 1969).

The following criteria were used in diagnosing CMV infection: (1) positive seroconversion or a 4-fold increase in CMV complement fixing antibody on parallel titration; (2) isolation of CMV; (3) finding of cytomegalic cells in lung sections on autopsy.

SEREOLOGICAL STUDIES

A representative collection of sera with a sample from before or very shortly after transplantation and at least monthly samples thereafter for the duration of the study period or until death, was available from 34 patients. At least a 4-fold increase in complement fixing antibody (CF) was demonstrated in 29. In ten patients no CF antibodies against CMV were detectable in the initial sera, but in seven of these it was possible to demonstrate a low titre of virus neutralizing (NT) antibodies. Thus infection may have been primary in three patients; in the others it was probably the result of the reactivation of a latent infection, although re-infection is a possibility. In most patients antibody rise took place in the second post-transplant month, but in some already during the first month, in some later and in one as late as seven months after transplantation. Maximum titre was usually reached early and held throughout the follow-up period, which was several years in some patients. In one patient, however, antibody again reverted to an inmeasurable level ten months after transplantation, but in spite of this it was possible to isolate virus from this patient’s urine on post-transplant days 420 and 469. Two of the five patients not showing antibody rise are now more than one year post-transplant.

In addition to the studies of CF antibody, an investigation of NT antibody against CMV strain AD 169 was performed in ten patients. Antibodies were demonstrated in all ten and in nine there was a rise in NT antibody parallel with that of CF antibody. In several patients this rise was delayed up to two months in relation to CF antibody.
CYTOMEGALOVIRUS INFECTION AFTER KIDNEY TRANSPLANTATION

Like Craighead et al. (1967), we found that CF antibody titre was higher in renal transplant recipients treated with immunosuppression than it is in previously healthy individuals with CMV infection. We did not find, however, as did the above-mentioned investigators, that it was common for the level of CF antibody to decrease prior to death.

VIRUS ISOLATION

CMV infection is characterized by the fact that patients excrete virus in saliva and urine for months or even years after infection. In this study we have concentrated mainly on the study of viruria. Isolation attempts were made by inoculating fresh urine on human embryonic fibroblasts cultured in 200 ml flasks. Cell cultures not showing cytopathogenic effects characteristic of CMV after 40 days were discarded as negative. Virus was isolated 16 times from the urine of 13 patients on 30 attempts. All urine isolations were made in patients who had demonstrated significant CF antibody rise. In one patient virus was isolated 26 days, in another first 290 days, after antibody rise. Virus has been isolated from one patient more than two years after serological evidence of infection.

CMV was isolated from the peripheral blood once on eight attempts from seven patients. This patient died on post-transplant day 83 without any rise in CF antibody, but there were CF antibodies in the initial serum.

The inoculation of a suspension of lung tissue on tissue culture from two patients where cytomegalic cells had been found on histological examination of the lungs resulted in the isolation of CMV in both cases.

HISTOLOGICAL STUDIES

A characteristic feature of CMV infection is the frequent presence of large (20 to 40 μ) cells with hypertrophied nuclei containing intranuclear inclusions. These cells are referred to as cytomegalic cells. Previous studies (Craighead et al., 1967; Rifkind et al., 1967), have shown that cytomegalic cells in renal allograft recipients with generalized CMV infection can be found in almost every organ of the body, but they are most commonly found in the lungs. On careful review of lung sections from the 17 patients in the autopsy series, cytomegalic cells were found in seven. The distribution of cytomegalic cells varied greatly from patient to patient. In some, several cells were found in a single small area, and in others they were seen diffusely throughout the lungs. Thus, some patients had a localized, others a diffuse CMV pneumonia.

Complement fixing antibodies were present at death in six of the seven patients, and in four there had been a significant rise in CF antibody in the post-transplant period. The patient with histological, but not serological evidence of infection died five weeks after transplantation at a time when most of the patients in our series have not yet shown antibody rise.

CMV infection can apparently take a chronic course in the lungs, as cytomegalic cells were found in the lungs of one patient (Fig. 1) 270 days after a significant rise in CF antibody had been demonstrated.

The ten patients where cytomegalic cells were not found in the lung sections died at varying periods of time after transplantation, but most of them within the first three months. Serological evidence of infection was present in six.

CLINICAL SYMPTOMS

A characteristic, febrile illness was seen in three patients in close association with rise in CF antibody. None of them had CF antibody before transplantation, but two had low titres of NT antibody. In one patient (Fig. 1) viruria was demonstrated several times and cytomegalic cells were found in the lungs at autopsy. Virus has also been isolated from the urine of an-
Fig. 1. Forty-three days after transplantation, this 18-year-old female renal allograft recipient developed fever which continued until the 71st day. Fever was inconstant, almost normal in the morning and 38–40°C in the evening (average daily temperature is given in the figure). There was headache, mild nausea and malaise during the first week of fever. A dry cough was present, but the chest was clear to percussion and auscultation. Chest X-ray revealed increased pulmonary vascular markings; films taken before and after this febrile illness were interpreted as normal. There was a fall in leucocyte count together with a relative lymphocytosis. Serum glutamic oxaloacetic transaminase measured 46 units nine days after the onset of fever and was below 32 units a week later. Graft function and general condition remained good throughout. Serological tests for influenza, ornithosis and toxoplasmosis were negative as were Paul–Bunnell and cold agglutinin reactions.

A chronic vascular allograft reaction developed nine months after transplantation which proved impossible to control, and the patient died in uraemia 329 days after transplantation. Cytomegalic cells were found in the lungs on autopsy and CMV cultured from lung tissue.

other, but not yet from the third. This illness with fever, malaise, and lymphocytosis has not previously been reported as a manifestation of CMV infection complicating immunosuppressive therapy, but such an illness is a common expression of the disease among normal, healthy adults (Klemola et al., 1967; Carlström et al., 1968). Two patients had a dry cough at the start of clinical illness and perhaps they had a CMV pneumonitis. Slight serum oxaloacetic transaminase elevation was seen in two, but jaundice was not observed. Nodular densities similar to those described by Rifkind et al. (1967) were seen on chest X-ray in two of the patients with autopsy evidence of CMV pneumonia, but it is difficult to ascribe this finding to CMV as both had bacterial pneumonia as well. Evidence of an acute, diffuse CMV pneumonia was found on autopsy in three patients and all had clinical and radiological signs of pneumonia before death. However, autopsy also revealed extensive bacterial pneumonia in all three and, therefore, it is uncertain what role CMV played in symptomatology.
Summary

Reported here are the results of a comprehensive serological, virological and histological study of the incidence and clinical significance of cytomegalovirus infection among 36 renal allograft recipients in the Aarhus series. We found evidence of infection in 33 patients for an incidence of 91%. In the majority of patients, infection occurred during the first two months after transplantation. It was also in this period that symptoms of infection were seen, in some presenting as an acute pneumonia, in others as a febrile illness.

REFERENCES


