RENAL CHANGES IN CYTOMEGALOVIRUS INFECTION

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Summary

Renal biopsy was performed in 20 graft recipients to characterise the histological features associated with poor renal function concomitant with cytomegalovirus infection (CMV). Eight patients presented with proteinuria, three had microscopic haematuria at onset, and five were hypertensive. Infection was accompanied by clinical symptoms (fever, leucopenia, mild hepatic damage, or pneumonitis) in 15 patients. In all cases, serum creatinine was >2mg/dl.

All patients showed some glomerular alteration on biopsy, and vascular changes were the predominant feature in seven cases. IgM and complement (C_3) were found in the glomeruli of five of six patients studied by immunofluorescence.

Serum creatinine was below 2mg/dl at ten to 26 months following the infectious episode in four patients and between 2–3mg/dl in three patients. The remaining 13 developed irreversible rejection and end-stage renal failure. We conclude that CMV, the most commonly recognised viral infection following transplantation, can cause renal changes, both glomerular (CMV glomerulopathy) and vascular (transplant vasculopathy), which may induce poor graft function.

Introduction

Cytomegalovirus (CMV) is the most commonly recognised infection in the first six months after renal transplantation [1]. The natural history and possible clinical impact of CMV infection in recipients of cadaveric renal transplants are the subject of increasing attention and study. CMV usually appears one to four months after transplantation. It can cause several symptoms of infection, may predispose toward superinfection, and might be a factor in allograft dysfunction and graft survival rate [2].

The mechanism by which CMV affects graft longevity is not established. Some evidence suggests that CMV infection may produce specific renal lesions; glom-

erular changes have been described in normal kidneys of infected patients as well as in transplanted grafts [3,4]. Other investigators believe that CMV infection merely stimulates a non-specific immune response which also acts against the allograft [5]. This study was designed to help clarify the role of CMV in allograft rejection, by analysing the incidence, severity, and characteristics of renal changes observed in transplanted patients with CMV infection.

Patients and methods

Two hundred and ninety-six patients receiving cadaveric transplants were studied during the period from April 1978 to December 1981. All were examined clinically for CMV infection. One hundred and thirty-nine patients underwent renal biopsy, and 20 of these met the criteria for CMV infection.

CMV virus was considered to be present when a fourfold or greater rise in complement fixing antibody titres was observed and when the virus was isolated from the patients. Antibody titre was also determined by the anticomplement immunofluorescence technique (ELISA). Virus was isolated on human embryonic lung fibroblasts [6].

An active clinical infection was diagnosed when at least one of the following symptoms occurred within three weeks of virological diagnosis and which could not be attributed to other factors: fever, leucopenia (total peripheral leucocyte count $<4000/mm^3$ on successive days), or an elevation of transaminase or bilirubin for several days. Diagnosis of pneumonia was based on appearance of radiographic infiltrates and clinical findings.

For the patients biopsied, interstitial, vascular, and glomerular changes were evaluated separately and classified in four different grades as follows: no changes, minimal, moderate, or severe. The following morphology was evaluated for renal changes:

1 Tubulo interstitial abnormalities –cellular infiltration, fibrosis, oedema, and/or haemorrhages.

2 Acute or chronic vascular changes – thickening or initial swelling, cellular proliferation, necrosis at the vessel walls or arterial occlusion and fibrosis.

3 Glomerular changes – capillary occlusion, cellular infiltration (endothelial or inflammatory cells), mesangial cell proliferation, and basement membrane abnormalities.

Immunosuppressive medication consisted of prednisone and azathioprine, antilymphocyte or antithymocyte globulin, and methylprednisolone.

Results

Clinical Symptoms

Twenty patients met the criteria for CMV infection, including isolation of CMV from urine in all cases. The mean time of detection was 2.3 months after transplant.

Low CMV antibody titres were present in the pre-transplant serum of all but two of the patients. A sharp increase, at least fourfold, was observed in 18 of the 20 patients. The earliest rise in serum antibody titre occurred 28 days following transplantation; the longest interval between transplantation and antibody increase was four months.

Fever and arthralgia were the most commonly associated symptoms. Liver dysfunction occurred in seven patients with development of mild transient elevation in transaminase. Pulmonary infiltrates were present in four cases. In 14 cases, CMV infection was also associated with leucopenia, 13 were observed prior to the rise in serum antibody titre.

Graft biopsy

All patients showed some glomerular changes on biopsy. Nine showed interstitial changes, seven vascular changes, and one mild infiltration. Immunofluorescence demonstrated IgM and complement (C_3) in the glomeruli of five of six patients (Table I).

TABLE I. Relationship of CMV infection to clinical complications and histological changes (Graft biopsy in patients with active virus infection) n = 20

Clinical findings		Histological changes	
Serum creatinine elevation	20 (100%)	Glomerular	20 (100%)
Fever	18 (90%)	Interstitial	9 (45%)
Arthralgia	11 (55%)	Vascular	7 (35%)
Leucopenia	14 (70%)	Mild infiltration	1 (5%)
Hepatic dysfunction	7 (35%)		

Outcome of the graft

Poor graft function was observed in all 20 patients and was irreversible in 13. Serum creatinine remained below 2mg/dl at 10–26 months following the infectious episode in four patients and between 2–3mg/dl at 14–24 months in three patients. The remaining developed irreversible rejection and end-stage renal failure.

The influence of the development of active CMV infection upon graft survival is shown in the life table analysis (Figure 1). The one year survival rate of all cadaver grafts (n = 296) and of those grafts whose recipients had clinical active infection were 58 per cent and 30 per cent respectively.

Discussion

It is not clear whether CMV infection is merely a clinical complication for transplanted patients or is a causative agent of renal damage. All CMV patients in our

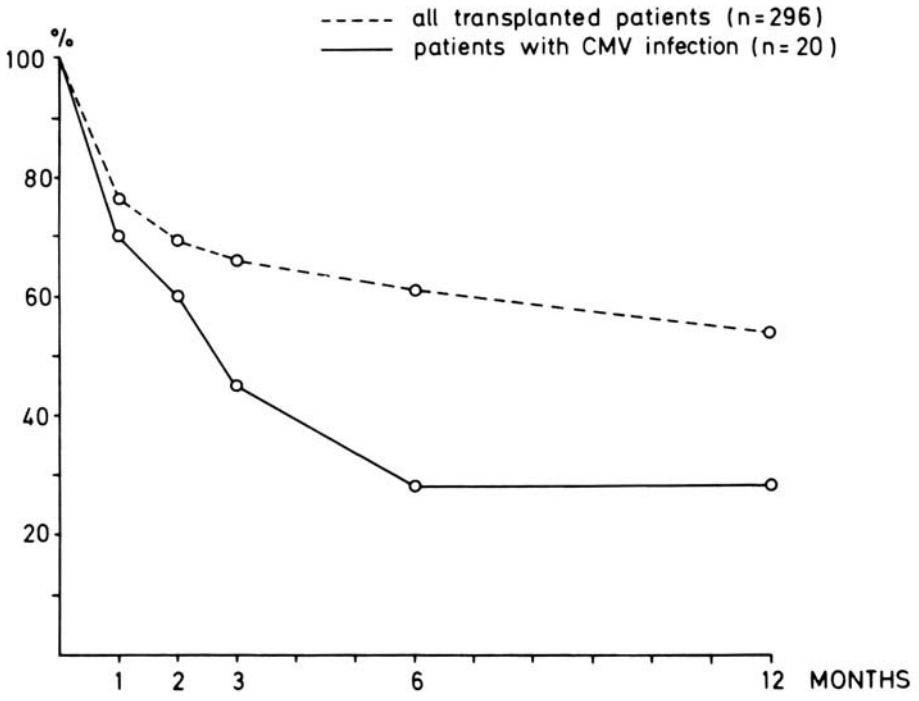

Figure 1. Cadaver graft survival rates

study exhibited both deterioration of renal function and histological damage. The decreased graft survival in this group strongly suggests that CMV infection damages renal tissue and reduces the prospects for allograft survival. Interestingly however, no clear-cut differences were observed between CMV patients who later rejected and those who did not.

Two mechanisms could be responsible for the poor renal function in CMV patients: i) the virus infection mainly stimulates the overall immune response which includes rejection, or ii) the CMV infection may have caused renal damage per se by deposition of immune complexes of virus and/or antiviral antibodies or by direct infection of the kidney.

The clinical and histological symptoms described here provide some evidence that CMV acts to stimulate immune response and thereby foster rejection.

In conclusion, it is quite evident that the development of active CMV infection is a serious deleterious complication to renal graft survival. The mechanisms remain uncertain but rejection secondary to heightened immunoactivity probably accounts for the majority of the adverse outcome. Diagnosis of a true glomerulonephritis will depend upon a more precise definition of the renal lesions caused by the virus.

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