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CLINICAL STUDY

Cytomegalovirus Disease in Renal Transplant Recipients: A Single-Center Experience

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Cytomegalovirus (CMV) disease is an important complication and an independent risk factor for acute rejection and recipient morbidity-mortality. The aim of this study was to review the results of CMV disease in renal transplant recipients. *Method*. We have retrospectively analyzed CMV disease in 120 renal transplant recipients and recorded the demographic features, clinical manifestations, and immunosuppressive regimens. *Results*. Twenty-nine recipients (24.1%) developed CMV disease after a median interval of 2.8 ± 2,6 months from transplantation. CMV disease developed in 36.3% of recipients who received basiliximab as induction therapy and 21.4% of recipients who were treated with anti-thymocyte globulin (ATG). The most commonly used immunosuppressive regimen was cyclosporine-A (CsA)-based (79.3%). The mean cumulative steroid dose until the diagnosis was 3,600 mg methyl prednisolone per patient. Malaise, fever, and diarrhea were the most common symptoms. Gastritis, pneumonia, and transaminitis were the most commonly seen end-organ involvements. Frequent laboratory findings were leukopenia (34.5%), increased serum creatinine level (34.5%), and leukocytosis (20.7%). We performed renal biopsy to seven patients and detected acute rejection in four patients. In 25 patients, immunosuppressive treatment was modified. Relapsing CMV disease was seen in seven patients. *Conclusion*. In our study, CMV disease was seen in recipients who were treated with basiliximab, a finding similar to recipients who were treated with ATG.

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Keywords cytomegalovirus disease, kidney transplantation

Cytomegalovirus (CMV) is one of the most important infections in renal transplant recipients.[1] The incidence and severity of CMV disease depend on the immunosuppressive regimen, CMV serostatus of the donor and recipient, and the type of transplanted organ. About one-quarter of renal transplant recipients developed CMV disease.[1] Patients with CMV disease may present with fever, leukopenia, or symptoms associated with organ involvement, including hepatitis, pneumonia, pancreatitis, colitis, meningoencephalitis, and myocarditis. CMV disease is an independent risk factor for acute rejection within the first 100 days and for recipient mortality.[14] In addition, the incidence of diabetes mellitus is higher in renal transplant recipients who developed CMV disease.[5]

The aim of this study was to review the results of CMV disease in renal transplant recipients.

PATIENTS AND METHODS

This study is a retrospective analysis of CMV disease in 120 consecutive renal transplant recipients who received an allograft between the years of January 2000 and January 2007 in our center. Demographic data were recorded, including age, sex, induction therapy, immunosuppressive regimens administered until the diagnosis of CMV disease, symptoms and organ involvements, laboratory findings (e.g., serum creatinine level, serum transaminase levels, leukocyte, and thrombocyte count), acute rejection episodes, pathological findings, and modifications of immunosuppressive therapy after the disease. Primary prophylaxis against *Herpes viridae* was applied to all patients with acyclovir (600 mg/day) for six months after transplantation. Also, intravenous ganciclovir treatment for 15 days was given to all recipients during antithymocyte globulin (ATG) treatment as CMV prophylaxis. CMV disease was defined as positive CMV antigenemia in the presence of symptoms and laboratory findings expected in the course of CMV disease. CMV antigenemia was diagnosed by detection of CMV-pp65 antigen in peripheral blood leukocytes in all recipients. Laboratory findings before the disease and at the time of diagnosis were recorded. Leukopenia was defined as leukocyte count less than 4,000/mm^3, leukocytosis as cell count higher than 10,000/mm^3, and thrombocytopenia as cell count less than 150,000/mm^3 in peripheral blood. Transaminitis was defined as ALT >31 U/L and AST >32 U/L at the time of the diagnosis or during the disease, after exclusion of causes other than CMV disease. CMV end-organ diseases were diagnosed by biopsy and pneumonia by bronchioloalveolar lavage. Biopsy specimens were evaluated pathologically by light microscopy and by immunohistochemistry for CMV involvement. Renal biopsy was performed to seven patients with acute rejection. Renal biopsy specimens were also examined for CMV involvement.

RESULTS

Twenty-nine recipients (24.1%) developed CMV disease after a median interval of 2.8 ± 2.6 months (1st–15th month) from transplantation. A total of 36 cases of CMV disease were recorded. All of the donor and recipients undergoing living transplantation was CMV IgG seropositive. The serostatus for cadaveric transplantation were not available. The mean age was 46.0 ± 11.0 years (27–68 years). Twenty-two of the patients were men and seven were women. Seventeen of transplantations were from cadaveric, while 12 were from living donors.

Thirty-three of 120 recipients were treated with basiliximab while 42 with ATG as induction therapy. Ten recipients received basiliximab as induction therapy and ATG for treatment of delayed graft function and/or acute rejection. CMV disease developed in 36.3% of recipients who received basiliximab as induction therapy and 21.4% of recipients who received ATG ($p > 0.05$). Two of 10 recipients who were treated with both basiliximab and ATG developed CMV disease. CMV disease occurred in 17.1% of patients who did not receive induction therapy. Among recipients with CMV disease, 12 (41.4%) patients were treated with basiliximab and 9 (31.0%) with ATG as induction therapy. The most common immunosuppressive regimen was CsA-based (79.3%). The mean cumulative steroid dose until the diagnosis of the disease was 3,600 mg methyl prednisolone per patient. Malaise was the most common symptom, which was seen in 24 patients. Fever and diarrhea was seen in 13 and 11 patients, respectively. Five (17.2%) of the 29 recipients developed transaminitis, four (13.8%) developed CMV gastritis, two (6.9%) recipients developed pneumonia, and one (3.4%) patient developed colitis. Ten (34.5%) patients had leukopenia, and six (20.7%) developed thrombocytopenia. Also, in six (20.7%) patients, leukocytosis was detected. Mean serum creatinine level was 1.5 ± 0.4 (0.9–2.4) mg/dL before the disease, 1.9 ± 0.6 (1.3–3.6) mg/dL at the time of the diagnosis, and 1.7 ± 0.06 (0.8–4.2) mg/dL at the end of the treatment.

We performed renal biopsy in seven patients. The biopsy revealed acute rejection in four patients while one patient had borderline rejection. Renal viral involvement was not detected on any renal biopsy specimen.

All infected recipients were treated with intravenous ganciclovir 2.5–5.0 mg/kg q 12h according to creatinine clearance for 21 days. In 25 patients, immunosuppressive treatment was modified by decreasing dose. Calcineurin inhibitors and mycophenolate mofetil were the most commonly modified immunosuppressive drugs. In seven patients, relapsing CMV disease occurred. Three of them received basiliximab, while two recipients received ATG as induction therapy. There was no mortality and graft loss

Table 1
Demographic and background characteristics of recipients who developed CMV disease

	Percent (n = 29)
Sex	
Male	76 (22)
Female	24 (7)
Mean age (mean+SD)	46.0 ± 11.0
Donor status	
Cadaveric	59 (17)
Living	41 (12)
CMV serostatus in living before transplantation (D/R)	
Positive/positive	100 (29)
Induction therapy	
Basiliximab	41.4 (12)
ATG	31.0 (9)
Basiliximab+ATG	6.8 (2)
No induction	20.7 (6)
Maintenance immunosuppressive therapy	
CsA-based	79.3 (23)
Tacrolimus-based	6.9 (2)
Rapamycine-based	13.8 (4)

due to CMV disease in our series. Demographic characteristics of patients with CMV disease are shown in Table 1, and symptoms and organ involvements are shown in Figures 1 and 2, respectively.

DISCUSSION

CMV disease is an important complication after solid organ transplantation. The incidence of the disease after renal transplantation had been defined in previous studies.

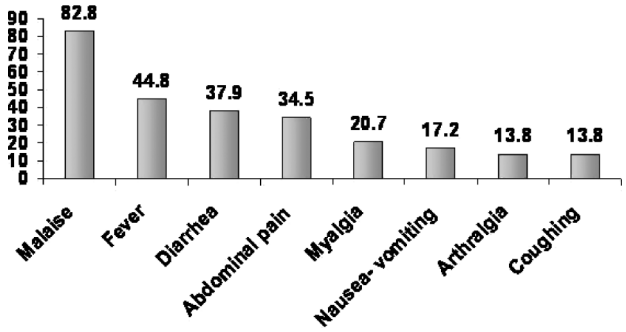

Figure 1. Incidence of symptoms (%).

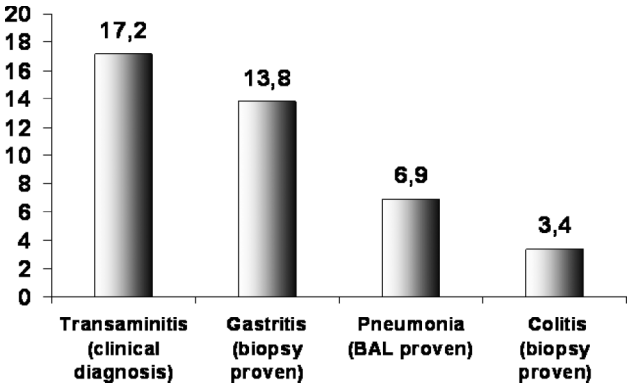

Figure 2. Incidence of organ involvement (%).

In a study among 451 renal transplant recipients, CMV disease occurred in 24% of patients during the first 100 days.[1] In our study, the overall incidence of CMV disease was 24%, which is similar with the previous reports. The median time between the transplantation and the presentation of sign and symptoms was 2.8 ± 2.6 months in our study, which supports previous studies.[6]

There are well-defined risk factors for CMV disease, such as CMV serostatus of the donor and recipient, the immunosuppressive regimen, and the type of transplanted organ. In our study, all of the donors and recipients undergoing living transplantation were CMV IgG seropositive. The serostatus for cadaveric transplantation were not available. The other important risk factor, immunoprophylaxis with ATG or basiliximab, was studied in a couple of studies. Lebranchu et al. found that there was significantly less CMV infection in the group treated with basiliximab. In the same study, CMV disease was seen in 6% and 12% of patients treated with basiliximab and ATG, respectively, but the difference was not statistically significant.[7] In the study of Mourad et al., 21.2% of patients treated with basiliximab and 41.5% of recipients treated with ATG developed CMV infection, the difference between the groups being statistically significant (p = 0.025).[8] In our study, CMV disease developed in 36.3% and 21.4% of recipients who received basiliximab and ATG as induction therapy, respectively. The difference was not statistically significant.

An accurate diagnosis of CMV disease is important because early treatment can prevent morbidity and mortality. Nemati et al. and Pour-Reza-Gholi et al. reported fever, nausea, and vomiting as the most commonly seen symptoms.[6,9] Farrugia and Schwab identified fever, malaise, and myalgia as the most common symptoms.[10] In our study, malaise, fever, and diarrhea were the most common symptoms, seen respectively in 24, 13, and 11 of 29 patients. The incidence of symptoms

seen in our patients is similar with the reports of previous authors.

Despite mild course of disease in most infected recipients, organ involvements can coexist. In the study of Abbott et al., pneumonia was seen in 17.1%, hepatitis in 4.2%, and complications of transplanted organ in 6.6% of renal transplant recipients hospitalized for CMV disease.[11] In the study of Durlik et al., the incidence of hepatitis, gastroenteritis, and pneumonitis was 46%, 27%, and 9%, respectively.[12] In our study, the most commonly involved organs are the stomach, lung, and colon. CMV gastritis is seen in four recipients (13.8%), pneumonia in two (6.9%), and colitis in one (3.4%). The incidence of organ involvements is variable among different studies. Thus, it is difficult to compare the results.

Elevated serum creatinine level, leukopenia, and thrombocytopenia are important laboratory manifestations of CMV disease.[6,12] Leukocytosis is as important as leukopenia in the diagnosis of the disease. In our study, the incidence of leukopenia and leukocytosis was 34.5% and 20.7%, respectively. Pour-Reza-Gholi et al. defined the most common laboratory findings as elevated serum creatinine level (71%), thrombocytopenia (43%), leukocytosis (22%), and leukopenia (21%). In that study, leukocytosis was as common as leucopenia.[6] In addition, an increase in serum creatinine level was detected in 10 of 29 patients, corresponding to 34.4% of recipients.

Patients were treated with intravenous ganciclovir, 2.5–5 mg/kg q 12h according to creatinine clearance for 21 days. All patients were treated successfully. We had no patient who was treated with CMV hyperimmunoglobulin additionally. No mortality and graft loss due to CMV disease was seen during the course of the disease. This finding, which is similar to other studies, indicates to us that CMV disease has a mild course and can be treated successfully. This can be explained by early diagnosis and treatment of the disease.

Despite the existence of well-defined risk factors, the disease can be seen in patients who show no risk factors. In this present study, CMV disease was seen in recipients who were treated with basiliximab as induction therapy, similar to those who were treated with ATG. Thus, in the presence of nonspecific symptoms like fever, malaise, and diarrhea; as well as clinical manifestations such as leukopenia, leukocytosis, and elevated transaminase and creatinine levels, CMV disease should be suspected, even in low-risk patients.

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