Does Cytomegalovirus Cause Glomerular Injury in Renal Allograft Recipients?

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Abstract. The case of a 16-yr-old woman who received an ABO-incompatible renal allograft for end-stage renal disease due to membranoproliferative glomerulonephritis type I is presented. The patient's posttransplant course was complicated by cytomegalovirus (CMV) infection and the rare finding of glomerular CMV inclusions on renal biopsy. This article focuses on the pathology and pathogenesis of glomerular injury associated with CMV infection in renal allograft recipients and also reviews the epidemiology, clinical implications, diagnosis and management of CMV infection in these patients. (J Am Soc Nephrol 8: 1801–1808, 1997)

Cytomegalovirus (CMV) is the major viral pathogen complicating renal transplantation (1). Although the histopathological features of CMV disease are well-characterized in many organ systems, there is less agreement on its renal manifestations, particularly in renal allograft recipients. In this article, we present the case of a 16-yr-old woman with an ABO-incompatible renal allograft whose posttransplant course was complicated by CMV infection and glomerular CMV inclusions on renal biopsy. We focus on the pathology and pathogenesis of glomerular injury in renal allograft recipients with CMV infection and also review the epidemiology, clinical implications, and current diagnostic and treatment modalities for CMV infection in this population.

Case Report

The patient was diagnosed with microscopic hematuria and proteinuria at 10 yr of age. Laboratory investigations revealed the following values: normal electrolytes; serum albumin, 1.5 mg/dl; complement 3 (C3), <10 mg/dl; C4, 37 mg/dl; fluorescent antinuclear antibodies (FANA), >1:64 (speckled pattern); creatinine clearance rate, 55 ml/min per 1.73 m²; and urinary protein, 5.9 g/24 h. Her renal biopsy was consistent with type I membranoproliferative glomerulonephritis (MPGN). At 15 yr of age, her renal disease progressed to end-stage and hemodialysis was initiated. A pretransplant evaluation indicated that the patient was ABO blood type O and CMV-negative. When she reached 16 yr of age, a decision was made to perform an ABO-incompatible renal transplant with her haploidentical, A1, CMV-positive brother as the donor. She was discharged from hospital on the 14th posttransplant day with a serum creatinine level (sCr) of 0.8 mg/dl.

On posttransplant day 105, the patient was readmitted to hospital because of a rise in her sCr to 1.5 mg/dl. She was afebrile. Cultures and titers for infection were obtained, and a percutaneous renal allograft biopsy was performed to rule out rejection. Investigations demonstrated seroconversion from CMV-negative pretransplant to CMV-positive posttransplant. CMV shell vial assays of her blood and urine were also positive. Her renal allograft biopsy showed mild acute tubulo-interstitial rejection, recurrent type I MPGN, and glomerular epithelial intracytoplasmic inclusions with a characteristic owl-eye appearance (Figure 1). Glomerular capillary intracytoplasmic CMV inclusions were seen on electron microscopy (EM) (Figure 2). Because of the CMV disease, the treatment of the acute rejection was postponed. Azathioprine was discontinued and a 14-d course of intravenous ganciclovir (5 mg/kg per dose twice daily) was initiated. Her sCr remained elevated at 1.2 mg/dl. Oral acyclovir (40 mg/kg per d divided into four doses) was started at the end of intravenous ganciclovir therapy. A repeat biopsy revealed a marked reduction in the CMV inclusions and a persistent focal interstitial mononuclear infiltrate with tubulitis. Azathioprine (2.5 mg/kg per d) was resumed and her prednisone (2 mg/kg per d) was recycled. The patient was discharged after 16 d of hospitalization, with a sCr of 1.2 mg/dl. She is now more than 6 yr past the date of transplant and has a sCr of 1.0 to 1.2 mg/dl.

Pathology and Pathogenesis of Glomerular Injury in Renal Allograft Recipients with CMV Infection

This case illustrates the need for renal biopsy in patients with acute renal allograft dysfunction; a dual process of acute rejection and CMV disease was present. Does CMV cause a specific glomerular lesion in renal allograft recipients? Richardson et al. originally reported a distinct glomerulopathy in renal allograft recipients with CMV viremia (2). In their study, 14 patients underwent percutaneous renal biopsy for acute allograft dysfunction. Seven of the 14 patients had CMV...
viremia, four patients had CMV infection without viremia, and three patients had no evidence of CMV infection. Four of the seven patients with CMV viremia had a unique lesion on light microscopy, which was characterized by endothelial cell hypertrophy or necrosis, narrowing or obliteration of capillary lumens, fibrillar deposits in glomerular capillaries, mild segmental hypercellularity, and mononuclear cell infiltration without tubular changes. Immunofluorescence microscopy (IF) revealed deposition of immunoglobulin G (IgG), IgM, and C3 along the glomerular basement membrane and within the mesangium. One specimen was available for the examination of CMV antigens by IF; anti-CMV antibody staining was observed within glomerular capillaries. No viral inclusions were found on EM. The authors concluded that CMV viremia is capable of inducing a glomerulopathy distinct from acute tubulointerstitial or vascular rejection (2). Tazoun et al. documented similar lesions in patients with renal allograft dysfunction; all eight patients had clinical evidence of CMV infection (3). The lesions contained large numbers of T lymphocytes, particularly the CD8+ subset. Class II major histocompatibility complex (MHC) antigens (HLA-DR) were expressed on intraglomerular mononuclear cells. The investigators hypothesized that CMV infection may produce a distinct form of glomerular T cell–mediated injury (3). Rao et al. reported the association of immunotactoid glomerulopathy in a renal allograft recipient with CMV infection. The lesion resolved with ganciclovir therapy and the withdrawal of immunosuppression (4).

The existence of a CMV-associated glomerulopathy has been questioned, however, by Herrara et al., who studied four different groups of immunocompromised patients with CMV infection, including seven with renal allograft dysfunction (5). In all seven patients, biopsy specimens demonstrated glomerular pathology similar to the changes described by Richardson et al. Nevertheless, IF failed to show anti-CMV antibody deposition. In addition, no viral particles were detected on EM. The authors suggested that the glomerular changes represented a form of acute transplant glomerulopathy resulting from antiendothelial antibody injury or a protracted, early, or unresolved form of acute vascular rejection (5).

Other investigators have also questioned the validity of the Richardson et al. findings. Harmon et al. showed that this glomerulopathy occurred in only seven of 56 renal allograft recipients with a clinical diagnosis of CMV disease. Three of the seven patients with this lesion were not viremic (6). Anderson et al., using immunohistochemistry and in situ hybridization on 15 biopsy specimens from viremic renal allograft recipients with glomerulopathy, found no evidence of CMV antigens or DNA (7).

This case demonstrates glomerular epithelial and capillary
intracytoplasmic CMV inclusions on light microscopy and EM. Payton et al. previously reported glomerular CMV inclusions on renal allograft biopsy. The inclusions were identified by light microscopy and confirmed by immunohistochemistry and in situ hybridization (8). Cameron et al. observed tubular epithelial CMV inclusions with light microscopy and EM in a biopsy specimen from a renal allograft recipient with CMV infection 21 months posttransplant. The patient had no allograft rejection (9). All of these rare lesions resulted from direct viral invasion. Because they did not resemble the glomerulopathy reported by Richardson et al., it is unlikely that CMV-associated glomerulopathy results from a direct cytopathic effect of the virus (10).

Instead, Rubin has proposed that CMV may produce glomerular injury through an indirect interaction with MHC antigens (10). Acute renal allograft rejection is characterized by T cell activation and the elaboration of inflammatory cytokines such as γ-interferon. This cytokine is capable of upregulating MHC antigens on renal parenchymal cells, resulting in immunologically mediated injury (10). Grundy et al. have shown that CMV infection increases cytoplasmic and cell-surface Class I MHC antigens in cultured fibroblasts and that this effect is mediated partly by β-interferon (11). Ustinov et al. reported that rats infected with the virus demonstrated simultaneous CMV antigen and Class II MHC antigen expression in the kidney (12). In human renal allograft recipients, van Es et al. found that CMV infection was associated with Class II MHC antigen upregulation on CD8+ lymphocytes. Patients with CMV infection had increased HLA-DR expression, which correlated with the onset of clinical symptoms and normalized with the resolution of the infection (13). Some investigators speculate that CMV infection results in an additional source of interferons that enhance MHC antigen expression and immunologically mediated injury, producing the inflammatory lesions seen in CMV-associated glomerulopathy. The CD8+ lymphocyte may act as the primary effector (1,3,10).

Other indirect cytokine-mediated effects may also contribute to this process. In addition, a more direct form of immunologic injury involving sequence homology between CMV and MHC antigens may be operative (1). Why only a minority of viremic recipients manifest CMV-associated glomerulopathy is unclear (3); the non-uniform appearance of this injury may in part be explained by differences in individual host tissue responses, immunosuppressive regimens, and anti-viral prophylactic and treatment strategies. Morphological findings attributed to CMV infection in renal allograft recipients are summarized in Table 1.

**Epidemiology and Risk Factors**

Two patterns of CMV infection are recognized in renal allograft recipients. Primary infection occurs in a previously uninfected (seronegative) recipient. In this situation, the virus

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**Table 1. Renal allograft morphology in cytomegalovirus (CMV) infection (references 2 through 9)**

<table>
<thead>
<tr>
<th>Author</th>
<th>Morphology</th>
<th>Conclusion</th>
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<tr>
<td>Richardson et al.</td>
<td>Endothelial cell swelling or necrosis; narrowing or obliteration of capillary lumens, fibrillar deposits in glomerular capillaries, mild segmental hypercellularity; mononuclear cell infiltration; anti-CMV glomerular capillary staining (one specimen); no CMV inclusions</td>
<td>Cytomegalovirus-associated glomerulopathy</td>
</tr>
<tr>
<td>Tauzon et al.</td>
<td>As above, disproportionate number of CD8+ lymphocytes within glomeruli</td>
<td>CMV-associated glomerulopathy resulting from T lymphocyte activation</td>
</tr>
<tr>
<td>Rao et al.</td>
<td>De novo immunotactoid glomerulopathy with resolution upon recovery from CMV infection</td>
<td>Association of active CMV infection and glomerulonephritis</td>
</tr>
<tr>
<td>Herrera et al.</td>
<td>Pathology similar to Richardson et al. findings; no CMV inclusions</td>
<td>Acute rejection; anti-endothelial antibodies or vascular rejection?</td>
</tr>
<tr>
<td>Anderson et al.</td>
<td>CMV antigen or DNA in four seropositive patients; no CMV antigens or DNA in 15 patients with glomerulopathy</td>
<td>No correlation between CMV infection and glomerulopathy</td>
</tr>
<tr>
<td>Payton et al.</td>
<td>CMV inclusions in glomerular and peritubular capillary endothelial cells and tubular epithelial cells on light microscopy; confirmed by immunohistochemistry and in situ hybridization</td>
<td>Findings represent direct viral invasion</td>
</tr>
<tr>
<td>Cameron et al.</td>
<td>Tubular atrophy; interstitial mononuclear infiltrates; tubular epithelial CMV inclusions on light microscopy and electron microscopy</td>
<td>Tubulointerstitial lesions resulting from a direct cytopathic effect of CMV</td>
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is generally acquired in two ways: via renal allografts from seropositive donors harboring latent CMV or through blood products contaminated with leukocytes infected with latent virus. Rarely, a CMV-negative recipient may develop primary CMV infection during intimate contact with an infected individual. Secondary infection occurs in previously infected (seropositive) individuals. There are two types: reactivation infection, which occurs in a seropositive recipient who reacts to endogenous latent virus, and reinfection, which develops when a seropositive recipient acquires a new strain of latent virus from a seropositive donor that subsequently becomes reactivated (1,14).

Certain factors are associated with an increased risk of CMV infection in this population. The most important variable is the donor/recipient immunologic status for the virus (1). Primary CMV infection is most likely to occur in seronegative recipients of seropositive donor allografts (D+R−) (14). Pediatric renal allograft recipients are at particularly high risk for primary infection because they have the lowest incidence of CMV seropositivity (10). The second most important risk factor is the recipient’s net state of immunosuppression, determined by the characteristics of the immunosuppressive regimen (type, dose, duration, timing of administration) and various host factors (uremia, neutropenia, infection with other immunomodulating viruses) (14). Unquestionably, the most potent reactivators of latent CMV are antilymphocyte antibodies. Renal allograft recipients receiving either polyclonal or monoclonal preparations have both an increased incidence of CMV viremia and an increased incidence and severity of CMV disease (1). Similarly, other factors associated with an increased state of immunosuppression (acute rejection, cadaver donor, HLA mismatching) may indirectly predispose the renal allograft recipient to CMV infection (14). Finally, some HLA antigens have been implicated in the development of CMV infection after renal transplantation (14), although the mechanism of this relationship is unclear. The risk factors for CMV infection in renal allograft recipients are presented in Table 2.

**Clinical Implications**

Active CMV infection is characterized by viral replication; it may be primary or due to reactivation and symptomatic or asymptomatic. CMV disease is symptomatic and defined by tissue invasion (14); it produces both direct and indirect clinical effects (1). Direct effects consist of clinical infectious disease syndromes manifesting most commonly as pneumonia, hepatitis, and gastrointestinal ulcers in the first 1 to 4 months after transplant, and chorioretinitis as a late complication (1). Other rare clinical manifestations include myocarditis or pericarditis, pancreatitis, cholecystitis, encephalitis, transverse myelitis, Guillain-Barré syndrome, and adenitis (1,14). An important indirect effect is immunomodulation, which increases the risk of life-threatening opportunistic infection with organisms such as Gram-negative bacilli, *Pneumocystis carinii, Listeria monocytogenes, Cryptococcus neoformans, Aspergillus* and *Candida* species (1). Other indirect effects of CMV infection are the possible roles in certain types of malignancy (primarily Kaposi’s sarcoma in patients with AIDS) and renal allograft rejection (1). Factors that predispose the renal allograft recipient to CMV disease include viremia, primary infection, reinfection, inability to mount an antibody (IgM) response, and antilymphocyte antibody therapy (14).

**Newer Diagnostic Techniques**

Diagnostic testing is based on either the evaluation of the immune response (serology) or the identification of the intact virus or viral proteins in the clinical specimen (viral detection).

**Serology**

Serologic assays have limited utility in the rapid diagnosis of CMV infection for several reasons. First, CMV viremia actually precedes a rising IgM titer. In addition, some immunocompromised patients are incapable of generating antibody to the virus. Furthermore, patients with asymptomatic reactivation may have elevated IgM titers. Thus the primary role of CMV serology in renal transplantation lies in the evaluation of donor and recipient IgG status to determine the potential risk of primary infection (1).

The reference standard for CMV antibody serology is the glycine-extracted complement-fixation assay, which measures antibody binding to CMV antigen isolated from fibroblasts infected with a common laboratory strain (AD169) (15). Alternative clinical laboratory methodologies include IF, enzyme-linked immunoassay, radioimmunoassay, and latex and indirect agglutination (15).

**Viral Detection**

The hallmark of the diagnosis of active CMV infection is the demonstration of the virus in clinical specimens (blood, urine, and respiratory secretions) and/or tissues. Viral detection techniques include conventional viral isolation, antigenemia assays, immunohistochemistry, *in situ* hybridization, and DNA amplification (15). Viral isolation involves the incubation of the inoculum with fibroblast monolayers and the subsequent demonstration of a CMV-specific cytopathic effect in 1 to 2 wk (and up to 6 wk in patients with low levels of the virus) (1,15). A major advance in viral detection is the shell vial technique, in which centrifugation of the specimen onto a flat fibroblast monolayer enhances viral absorption, resulting in a fourfold increase in CMV infectivity. IF with a monoclonal antibody to the 72-kD major intermediate-early protein permits the detection of the virus within 24 to 48 h (15). Thus this test does not
Table 3. Diagnostic strategies for CMV infection in renal allograft recipients (references 1, 7, 15 through 20)

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Comment</th>
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<tr>
<td>Serology</td>
<td>Primary utility lies in evaluation of donor/recipient CMV antibody status to predict risk of primary infection</td>
</tr>
<tr>
<td>Viral detection (blood/urine/respiratory secretions)</td>
<td>Relies on observation of CMV cytopathic effect which requires 1 to 2 wk (and up to 6 wk) to visualize; specimens include blood, urine, and respiratory secretions (rarely tissue)</td>
</tr>
<tr>
<td>viral isolation</td>
<td>Rapid technique (24 to 48 h), which does not rely on visualization of cytopathic effect; used on blood, urine, and respiratory secretions</td>
</tr>
<tr>
<td>shell vial assay</td>
<td>Even more rapid than shell vial assay (&lt;5 h); used on peripheral leukocytes</td>
</tr>
<tr>
<td>The's antigenemia assay*</td>
<td>Exquisitely sensitive with potential for false-positive results; rapid; precedes CMV viremia and disease; may be quantitative; potential for therapeutic monitoring; used on plasma</td>
</tr>
<tr>
<td>PCR</td>
<td>Non-specific; all tissue-invasive herpesvirus infections characterized by inclusions</td>
</tr>
<tr>
<td>Viral detection (tissue)</td>
<td>Detects subcellular levels of CMV antigen</td>
</tr>
<tr>
<td>histopathology (light microscopy and electron microscopy)</td>
<td>Detects CMV DNA</td>
</tr>
<tr>
<td>immunohistochemistry/immunofluorescence</td>
<td>Exquisitely sensitive; detects CMV DNA; may be quantitative with potential for therapeutic monitoring</td>
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<tr>
<td>in situ hybridization</td>
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<td>PCR</td>
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*From reference 16.

rely on the direct visualization of a cytopathic effect as the diagnostic end point (14). Although this methodology accurately detects CMV antigens in urine and respiratory secretions, it is much less sensitive for CMV viremia, because the leukocytes contained in buffy coat specimens are toxic to fibroblasts (15).

Because CMV viremia is the most reliable marker for the progression to CMV disease (1), early diagnosis of CMV antigenemia is critical for the initiation of therapy. The's antigenemia assay (see reference 16) permits even more rapid detection of CMV antigens (within 5 h). In this assay, leukocytes from buffy coat specimens are isolated and centrifuged onto slides, labeled with monoclonal antibodies to a late structural antigen (65-kD lower matrix phosphoprotein, pp65), stained with immunoperoxidase, and counterstained with hematoxylin, permitting the enumeration of positive cells (16).

Recently, the polymerase chain reaction (PCR) has been utilized to detect CMV antigens directly in peripheral blood leukocytes (15,16). The PCR was originally developed for the selective amplification of DNA sequences. Using oligonucleotide primer pairs, target DNA is amplified for 30 to 40 cycles, resulting in exponential replication. It is estimated that this technology is capable of detecting one CMV virion in 40,000 cells (17). However, this exquisite sensitivity may also give rise to false-positive results. Conversely, false-negative results can potentially occur with genetically heterogenous strains (15). Schafer et al. developed a competitive nested PCR technique that permits the quantification of CMV DNA transcripts in peripheral leukocytes of renal allograft recipients. Patients with active CMV infection had 8000 to 10,000 DNA copies, whereas asymptomatic patients had only 200 to 900 of such copies (18). Thus this technology has the potential for therapeutic monitoring.

CMV histopathology is recognized by intranuclear inclusions producing a characteristic “owl eye” appearance on light microscopy. Viral inclusions are also seen on EM. Neither of these features, however, is specific, because all tissue-invasive herpesvirus infections are characterized by this appearance (14). For CMV disease, in situ hybridization with CMV-specific nucleic acid probes and immunohistochemistry with monoclonal antibodies against CMV antigens permits the identification of the virus in infected tissue or cultured cells (15). Nast et al. used immunohistochemistry with antibodies against CMV early nuclear protein and DR antigen to differentiate CMV infection from AR in renal allograft recipients with graft dysfunction (19).

Finally, Chen et al. have utilized PCR with DNA primers encoding late antigens to detect CMV infection within renal
allografts. Importantly, PCR-positivity correlated directly with culture-positivity and/or seroconversion. In contrast, all PCR-negative patients were seronegative without active disease. CMV inclusions were only rarely detectable in the biopsy specimens (20). Diagnostic strategies for renal allograft recipients with CMV infection are outlined in Table 3.

**Management**

There are three approaches to the management of CMV infection in renal transplant recipients: viral prophylaxis; treatment of active infection; and, for the latter group, prophylaxis against opportunistic infections (10). Viral prophylactic strategies are aimed at the prevention of primary or secondary infections. To prevent the acquisition of new viruses, some centers recommend that seronegative renal allograft recipients receive only CMV-negative and leukocyte-poor blood products when transfusions are necessary (10, 14). This precaution is impractical, because the CMV-negative blood pool is limited. Another potential but controversial strategy is the protective matching of renal allografts (D−R−) to prevent primary infection. However, this approach threatens the already shortened supply of organs.

Other prophylactic strategies include the use of CMV-specific immunizations. Using the live-attenuated Towne vaccine in D+R− patients in a randomized, double-blind, placebo-controlled study, Plotkin et al. demonstrated a reduction in the severity of CMV disease (zero cases for the vaccinated group versus four or four cases for the placebo group, P < 0.03) (21). Nevertheless, the efficacy of a monovalent vaccine against considerable CMV strain variation remains to be determined (1). Passive immunization with CMV-immune globulin (CMVIG) has also been investigated as prophylaxis in renal allograft recipients. CMVIG is obtained from the blood or plasma of healthy donors containing high titers of naturally occurring CMV-antibody. Snyder et al., in a randomized, controlled study of 59 D+R− recipients administered CMVIG within 72 h of transplantation and continued to 16 wk after transplant, had a 65% reduction in the incidence of CMV disease, with the greatest attenuation occurring for leukopenia, fungal and parasitic opportunistic infections, thrombocytopenia, and hepatitis (22). However, CMVIG prophylaxis is expensive, inconvenient to administer repeatedly, and contains variable amounts of antibody (1). We do not routinely administer the Towne vaccine or CMVIG for CMV prophylaxis.

Antiviral chemoprophylaxis is currently the most widely utilized CMV preventative strategy in renal allograft recipients. Acyclovir, a deoxyguanosine analogue, was the first antiviral agent studied in renal allograft recipients. This agent requires in vivo phosphorylation before it is capable of competitive inhibition of CMV DNA polymerase (23). In a randomized, double-blind, placebo-controlled study at our center, Balfour et al. showed that a 12-wk course of high-dose acyclovir resulted in a marked reduction in the incidence of CMV disease (8% versus 29% for placebo controls; P < 0.002). High-risk D+R− patients had the greatest benefit, with only one of six patients receiving acyclovir prophylaxis developing CMV pneumonia, compared to seven of seven patients receiving placebo (P < 0.005) (24).

Ganciclovir [9-(1,3-dihydroxy-2-propoxymethyl) guanine], has a similar mechanism as acyclovir, but achieves a higher concentration of the phosphorylated form in infected cells (23). Short-term CMV prophylaxis with intravenous ganciclovir has been disappointing. In a randomized, controlled prospective study at our center, Dunn et al. compared the efficacy of a short-term ganciclovir-based prophylactic regimen (5 mg/kg per 12 h intravenously for 7 d after transplant or after anti-rejection therapy) and human immune globulin (Hlg/Minnesota CMV immune globulin; 100 mg/kg intravenously on days 1, 4, and 7 after transplant and after anti-rejection therapy) with long-term acyclovir prophylaxis (800 mg orally or 400 mg intravenously four times daily for 12 wk after transplant or 6 wk after rejection therapy) in 266 solid organ allograft recipients. Patients administered ganciclovir plus immune globulin had a higher incidence of CMV disease (32%) than those receiving acyclovir (21%, P < 0.03). Among those receiving ganciclovir and immune globulin, the highest incidence of CMV disease occurred in the D+R− subgroup (55%, P < 0.04) (25). However, the difference in outcome may have been attributable to the relatively shorter duration of therapy of ganciclovir and immune globulin. Although oral ganciclovir has recently received FDA approval for CMV prophylaxis in solid organ transplantation, there are no published reports of its utility in renal allograft recipients. Our center is currently investigating the efficacy of oral ganciclovir versus oral acyclovir as prophylaxis in solid organ allograft recipients.

Because D+R− patients are at high risk for developing CMV disease (1), we and other researchers administer both ganciclovir and acyclovir preemptively to this group (1). At transplantation, D+R− patients receive 7 to 14 d of intravenous ganciclovir followed by 10 to 11 wk of oral acyclovir for a total duration of 12 wk. For steroid-resistant rejection episodes requiring antilymphocyte antibody, these recipients are also given 7 to 14 d of intravenous ganciclovir and 4 to 5 wk of acyclovir thereafter for a total duration of 6 wk.

Ganciclovir is the mainstay of therapy in renal allograft recipients with active CMV infection. Dunn et al. reported a 89% 30-d cure rate in renal allograft and renal-pancreas allograft recipients with CMV disease treated with intravenous ganciclovir, although 21% of these patients relapsed, necessitating retreatment with the agent (26). We administer 14 d of intravenous ganciclovir followed by 10 wk of oral acyclovir (total duration, 12 wk) in all renal allograft recipients with CMV disease. Finally, measures to prevent opportunistic infections in renal allograft recipients with active CMV infection include the reduction or discontinuation of antilymphocyte antibody and/or azathioprine whenever possible and prophylaxis for P. carinii infection (10,14).

**Conclusion**

This case illustrates the rare finding of glomerular CMV inclusions on renal allograft biopsy. There are both direct and indirect types of glomerular injury in renal allograft recipients with CMV infection (10). Although the pathogenesis of the
latter is unknown, there are several lines of evidence to suggest that it is immunologically mediated with γ-interferon as the mediator and the CD8+ lymphocyte as the effector (3,10). Why only a minority of renal allograft recipients with CMV infection develop CMV-associated glomerulopathy is unknown (3,10). However, newer diagnostic and therapeutic strategies hold good promise for the rapid and effective clinical management of these patients.

Acknowledgments

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References


Pediatric Nephrology Training Program at the University of Minnesota

The Pediatric Nephrology Training Program at the University of Minnesota was established 30 years ago by Alfred Michael and Robert Vernier and has received continuous support from the National Institutes of Health. Eighty of the 93 fellows that have completed the three-year training program occupy academic positions in North America and other parts of the world. All forms of childhood renal disease are seen in our outpatient clinics and in the wards at the Fairview-University Medical Center and its affiliated hospitals. The pediatric renal transplant program, established by John Najarian, is one of the world’s largest and emphasizes transplantation of children under the age of two years. The basic three-year fellowship program provides 11 months of clinical experience and 25 months for clinical and/or laboratory research. Six months of the first year of the fellowship are divided into two blocks, which include four months running the inpatient and consult service and two months on the dialysis and transplantation service. Five additional months are spent in clinical rotations during the subsequent two years. Fellows receive training in all methods of renal replacement therapy, including dialysis, and continuous replacement therapy. Fellows follow a cohort of patients in outpatient clinics and on average perform 10 to 15 native kidney biopsies and 30 to 40 renal transplant biopsies during the three-year period. The research interests of the eight-member faculty focus on the molecular biology of basement membranes in health and disease (Alport syndrome, Goodpasture syndrome, diabetes mellitus, congenital nephrotic syndrome), pathogenesis of diabetic nephropathy, developmental biology of the kidney, transplant biology, and the molecular genetics of Alport syndrome. Clinical research interests include diabetic nephropathy, childhood hypertension, and issues related to end-stage renal disease and transplantation (growth, optimization of immunosuppressive strategies, opportunistic infection). Fellows may carry out research projects in any of the internationally renowned laboratories in the University of Minnesota Medical School.