Abstract

Objectives: Antibody-mediated rejection is a rare complication that often results in the loss of the kidney graft. Treatment options include plasmapheresis, intravenous immunoglobulin, and use of rituximab.

Materials and Methods: We retrospectively evaluated the data files from 86 pediatric renal transplant patients over the last 5 years. A biopsy was taken for each rejection episode.

Results: Seven patients (7.7%) developed antibody-mediated rejection. All patients with antibody-mediated rejection had histologic evidence of severe acute humoral rejection and extensive C4d staining in peritubular capillaries. Staining was diffuse (involving > 50% of peritubular capillaries) for 4 biopsies, and it was focal (involving < 50% of peritubular capillaries) for 3 biopsies. Twelve biopsies demonstrated at least 1 histologic feature associated with acute humoral rejection. Donor-specific antibodies were evaluated in recipients. The mean peak panel reactive antibody class 1 was 7.16% (range, 0%-86%). The mean time between rejection episodes and the transplant was 16.9 ± 13.5 months. All patients were treated with high-dose intravenous methylprednisolone and intravenous immunoglobulin. Three patients recovered renal function rapidly after this treatment. Donor-specific antibodies were negative in these patients. Five sessions of plasmapheresis were used simultaneously in these 4 patients. In 3 resistant patients, rituximab was prescribed after plasmapheresis and intravenous immunoglobulin. The presence of donor-specific antibodies was demonstrated in 4 patients. Two patients were refractory to antibody-mediated rejection treatment and lost their transplants. One patient had interstitial fibrosis and tubular atrophy during the 16th month after her antibody-mediated rejection. Graft survival in patients with antibody-mediated rejection at the end of 1 year was 71.4%.

Conclusions: Early diagnosis and treatment with plasmapheresis, intravenous immunoglobulin, and rituximab may resolve antibody-mediated rejection. Although effective therapy is available for acute antibody-mediated rejection, the allograft remains at risk for chronic antibody-mediated rejection and shortened survival.

Key words: Children, Renal transplant, Outcome.

Introduction

Antibody-mediated rejection (AMR) is one of the important complications of renal transplant that often results in the lost of the kidney graft, requiring a different therapy than standard T-cell–mediated rejection. Antibodies, B cells, plasma cells, and complement systems play a prime role in the pathogenesis. The diagnostic criteria of AMR are the demonstration of C4d in peritubular capillaries, inflammation, and/or tissue injury, and serologic evidence of circulating antibodies to donor human leukocyte antigen, or other antidonor endothelial antigens. Antibody-mediated injury of peritubular capillaries results in endothelial injury, with the loss of capillary patency, ischemia, and the proliferation of myofibroblasts leading to progressive interstitial fibrosis. The goal of treatment is to influence and
modify factors that play a role in the pathogenesis. Treatment options for this condition might include high-dose intravenous methylprednisolone, plasmapheresis, intravenous immunoglobulin (IVIG), and using rituximab. The anti-inflammatory and immunoregulatory actions of IVIG are modification of complement activation and cell-mediated immunity. Rituximab causes a profound and sustained depletion in the number of circulating B cells. A combination of pulse methylprednisolone, high-dose IVIG, and rituximab is recommended for treatment of AMR. New approaches of treating AMR include using the proteosome inhibitor (bortezomib) and eculizimab. We present the results of our patients with AMR.

Materials and Methods

We retrospectively evaluated data files from 86 pediatric renal transplant patients during the last 5 years. Medical records were used to identify these patients. Demographic data are noted, retrospectively. All protocols were approved by the ethics committee of the institution before the study began, and the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration.

Antibody-mediated acute rejection is determined by an increase in serum creatinine at least 20% above baseline serum creatinine, with histologic evidence of AMR defined by Banff criteria. Renal biopsy was performed on 24 patients because of the elevated creatinine levels during the routine follow-up, and AMR was proven by biopsy. Renal biopsies were graded using the Banff criteria. Suspect histologic findings for AMR were presence of acute tubular necrosis, presence of inflammatory cells in the lumen of peritubular capillaries, and fibrinoid necrosis in vessel walls or thrombi. C4d immunohistochemical staining was performed on each biopsy, and all evaluations were performed by a single pathologist.

Donor-specific antibodies in the recipients were detected through the use of a Luminex microsphere-based assay. Those were not detectable before transplant, but were present at the time of rejection.

Antibody-mediated rejection treatment consisted of combination therapy with methylprednisolone, intravenous immunoglobulin, plasmapheresis, and rituximab. Patients received different treatment modalities with different combinations. Methylprednisolone was given intravenously (30 mg/kg/d), for 3 days, consecutively. Intravenous immunoglobulin was given at a dosage of 2 g/kg, and rituximab was given at a dosage of 375 mg/m². Four courses of IVIG were given. The count of rituximab courses given were ranged from 2 to 4. Five sessions of plasmapheresis were performed under anticoagulant with fresh frozen plasma (1.5 plasma volumes).

Results

Seven patients (7.7%; 4 males, 3 females) developed AMR. The mean age of these patients was 12.40 ± 3.60 years old at the time of investigation. Six patients received a living-related donor allograft, and the remaining patient received the allograft from a deceased donor. The distribution of the number of the human leukocyte antigen mismatches was 1 and 2. Donor-specific cross-matches before transplant were negative in all patients. Anti-IL2 receptor blocker induction therapy was given to only 1 patient who had received an allograft from a deceased donor. Each individual received calcineurin inhibitors (cyclosporine or tacrolimus), mycophenolate mofetil, and prednisolone. There was no problem of adherence to treatment in these patients. The mean time between rejection episode and transplant was 16.9 ± 13.5 months.

Biopsies were performed for each rejection episode. Seven of 24 biopsies (29%) taken for acute rejection were compatible with AMR. All patients with AMR had histologic evidence of severe humoral acute rejection. All biopsies revealed capillaritis, tubular damage, peritubular capillary dilatation, glomerulitis, plasma cell infiltration, and extensive C4d staining in peritubular capillaries. Staining was diffuse (involving > 50% of peritubular capillaries) for 4 biopsies and it was focal (involving < 50% of peritubular capillaries) for 3. Twelve biopsies were demonstrated at least 1 of the histologic features associated with acute humoral rejection. Donor-specific antibodies demonstrated in 4 patients (class 1 and class 2 in 3 patients, and class 2 in 1) and progressively decreased after treatment. The mean peak PRA class 1 was 7.16% (range, 0-86).

Three patients received only high-dose intravenous methylprednisolone and IVIG. Donor-specific antibodies were negative in these patients, and AMR diagnosis was proven with biopsy. All biopsies revealed capillaritis, tubular damage, peritubular capillary dilatation, glomerulitis, plasma cell infiltration, and extensive C4d staining in peritubular
capillaries. Staining was focal in these patients (involving < 50% of peritubular capillaries). They recovered renal function rapidly after this treatment modality. Interstitial fibrosis and tubular atrophy proven with biopsy developed in 1 of them within 16th months after AMR. High-dose intravenous methylprednisolone and IVIG therapies supported with 5 session of plasmapheresis in 4 patients and renal function of 1 patient become normal. C4d staining in peritubular capillaries was diffuse (involving > 50% of peritubular capillaries) and donor-specific antibodies were positive in these patients. At rest, in 3 resistant patients to high-dose methylprednisolone, IVIG, and plasmapheresis, rituximab was prescribed. Two of these patients were refractory to AMR treatment and lost their grafts (Table 1). Graft survival in patients with AMR at the end of 1 year was 71.4%.

Table 1. Treatment Modality, Graft Loss, and Donor-Specific Antibodies

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Number of Patients</th>
<th>DSA Presence</th>
<th>Graft Loss</th>
<th>Renal Function Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone + IVIG*</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Methylprednisolone + IVIG + plasmapheresis</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Methylprednisolone + IVIG + plasmapheresis + rituximab</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: DSA, donor-specific antibody; IVIG, intravenous immunoglobulin

Discussion

Acute rejection is an important complication of renal transplant. Antibody-mediated rejection occurs less than cell-mediated rejection. Treatment of this disease must target underlying pathogenic mechanisms. The goal of treatment modalities for AMR is depleting B cells and plasma cells and eliminating the late donor-specific antibodies. We tried to determine the efficiency of treatment modalities for AMR.

Antibody-mediated rejection was identified in approximately 5% to 7% of patients and 12% to 37% of the biopsies taken for acute rejection. During 5 years of follow-up, 7.7% of our patients was developed AMR. One third of all of our biopsies demonstrated AMR. These data have shown that AMR is not a rare complication.

In Moure and associates’ study, graft survival of the patients with AMR was 62.5% at the end of 1 year. In our study, graft survival of patients with AMR at the end of 1 year was 71.4%. Donor-specific antibodies present at the time of acute rejection diagnosis is a poor prognostic factor for allograft survival. In our study group, donor-specific antibodies were demonstrated in 4 patients and 2 of them had lost their grafts. These patients with donospecific antibodies present did not respond to high-dose intravenous methylprednisolone and intravenous immunoglobulin therapy and further treatment modalities were needed for renal function recovery. Primarily, 5 sessions of plasmapheresis were performed on these patients. One patient responded to plasmapheresis with renal function recovery. The addition of rituximab might have improved outcomes in AMR. Rituximab therapy was required for the other 3 patients, and only 1 patient responded to a combination of high-dose intravenous methylprednisolone, intravenous immunoglobulin, plasmapheresis, rituximab. Although 1 patient responded to high-dose intravenous methylprednisolone and intravenous
Early diagnosis and treatment with high-dose intravenous methylprednisolone, plasmapheresis, intravenous immunoglobulin, and rituximab, although their efficiency is not clear, may resolve AMR. There is not a precise treatment protocol for AMR. Patients were not being treated with a definite protocol because of the retrospective design of this study. Antibody-mediated rejection treatment was chosen because of the clinical condition of the patient. This type of treatment chosen step-by-step may affect the success of the treatment and may fail in long term. Despite of effective therapy for acute AMR, allografts remain at risk for chronic AMR and shortened survival. Antibody-mediated rejection treatment protocol must be determined. Treatment protocol for AMR must include the suppression of the T-cell–dependent antibody response, the blockage of the residual alloantibody, the removal of donor-specific antibody, and the reduction of memory B cells. Treatment with high-dose intravenous methylprednisolone, intravenous immunoglobulin, plasmapheresis, and rituximab provide for these needs. Follow-up after AMR treatment consisting of only biochemical parameters (eg, creatinine) may cause misdiagnosis of chronic AMR. Protocol biopsy and donor-specific antibody screening may be helpful in selected cases.

References