Mini Review

Acute Cellular Rejection

Mohammad-Reza Ganji,[1] Behrooz Broumand[2]

[1]Department of Nephrology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Nephrology, Rasoul-e-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

Keywords. kidney transplantation, graft rejection, cellular immunity, immunosuppression

The incidence of acute rejection of the kidney allograft in the world has been around 15% during the period between 2001 and 2003. It is clinically defined as an elevation in the level of serum creatinine by more than 0.3 mg/dL and is diagnosed by kidney biopsy. On pathologic examination, the interstitium of the allograft is diffusely edematous and infiltrated by CD4 and CD8 lymphocytes. Tubulitis occurs when the lymphocytes and monocytes extend into the walls and lumina of the tubules. Presence of leukocytes determines infection or antibody-mediated rejection. Typically C4d staining is negative. Other causes of acute allograft dysfunction included prerenal factors, interstitial nephritis, infection, acute tubular necrosis, toxicity by drugs, and obstruction in the urinary tract. The primary diagnostic assessments include history, especially adherence to immunosuppressive therapy, physical examination, blood and urine laboratory tests, measurement of the serum levels of the drugs, and ultrasonography. Diagnosis of acute cellular rejection depends on biopsy, CD20 staining for refractory cases, negative C4d staining, presence of markers of activating lymphocyte, and proteomic study.
Treatment of acute cellular rejection in kidney transplant recipients include pulse steroid for the first rejection episode. It can be repeated for recurrent or resistant rejection. Thymoglobulin and OKT3 are used as the second line of treatment if graft function is deteriorating. Changing the protocol from cyclosporine to tacrolimus or adding mycophenolate mofetil or sirolimus might be effective. Prognosis depends on number of rejection episodes, the use of potent drugs, time of rejection from transplantation, and response to treatment.

IJKD 2007;1:54-6
www.ijkd.org

Acute rejection (AR) remains a major complication after kidney transplantation. Although the incidence of AR has declined with the advent of new immunosuppressive drugs, it is still around 15% worldwide.[1] Acute rejection usually manifests as an increase in serum creatinine, and less often, with hematuria, graft tenderness, and fever. Diagnosis can be made only by allograft biopsy. Other causes of acute allograft dysfunction include prerenal factors such as reduced effective arterial blood volume, transplant renal artery stenosis, interstitial nephritis, infections (bacterial and viral), acute tubular necrosis, recurrent or de novo glomerular diseases, calcineurin-inhibitor-induced toxicity, and urinary tract obstruction.[1] Assessment of acute allograft dysfunction includes history taking with especial attention to adherence to immunosuppressive treatment, physical examination, examination of the serum levels of immunosuppressive drugs, imaging studies by B-mode and Doppler ultrasonography, and blood and urine laboratory tests.

The short-term graft survival after treatment of

AR has been improved; however, the long-term outcome is not promising and AR remains a major risk factor for chronic allograft dysfunction.[2,3] Donor age, donor-recipient human leukocyte antibody mismatch, panel reactive antibodies (PRA), ethnicity, and delayed graft function have been shown to be associated with the risk of rejection.[4] The majority of graft lost cases after 4 to 6 months posttransplant are due to volume depletion, immunosuppressives, and urinary tract infection. Prompt diagnosis of pyelonephritis is mandatory, especially after the first year due to its strong association with graft loss.[5]

There are 2 types of AR that could occur either separately or together: cellular and humoral (antibody mediated). Alloreactive immune response is initiated at the interface of the graft's endothelium and the host's CD4, CD8, and natural killer cells.[6,7] Subsequently, type 1 helper T cells and CD8 lymphocytes release interferon-γ and interleukin-2 on alloantigen contact and augment the cellular immune response that leads to the activation of cytotoxic T lymphocytes, natural killer cells, and monocytes that infiltrate the graft. The type 2 helper T cells' response triggers the humoral response and formation of antibodies that bind to the endothelium and induce complement activation and tissue injury. Acute cellular rejection (ACR) is characterized by tubulitis that occurs when the lymphocytes and monocytes extend into the walls and lumina of the renal tubules, with associated degenerative changes of the epithelial cells. In cell-mediated vascular rejection that can be seen with tubulointerstitial rejection, the lymphocytes and monocytes undermine the swollen arterial endothelium, and with more advanced alloreactivity, arterial wall necrosis can occur. The activated T cells which mediate the AR can be shown to have upregulated expression of T-cell activating genes.[8] Interestingly, induction with alemtuzumab has been associated with a predominantly monocytic ACR and poor response to pulse steroids.[9]

Antibody-mediated rejection (AMR) is associated with neutrophilic margination in peritubular and glomerular capillaries and is typically C4d-positive on fluoroimmunoassay or immunochemistry. The importance of differentiating humoral rejection from ACR was illustrated by many studies[10,11]; Mauiyyedi and colleagues studied on patients diagnosed with ACR and found that half of them had a mild ACR that responded to pulse steroid treatment and the other half had a more severe ACR responded to OKT3 or antilymphocyte globulin. Graft survival at 6 months for patients in the two groups was 97%.[10] However, patients diagnosed as AMR had a 78% graft survival rate at 6 months. Treatment of the AMR has been successful with different combinations of mycophenolate mofetil, tacrolimus, plasmapheresis, anti-CD20, and intravenous immunoglobulin.[11]

Diagnosis of ACR depends on the pathology of specimens obtained by kidney allograft biopsy and different histologic examinations of the kidney tissue, including C4d staining. Noninvasive diagnosis of AR is not currently available. There are a few reports on the association of a positive staining for CD20 in refractory cases that may prompt treatment with Anti-CD20 antibody.[12] Furthermore, several other biomarkers in serum and urine have been proposed for prediction or diagnosis of AR, some with specification for ACR, none used in practice yet. The following are a summary of these markers: urine levels of chemokines CXCL9, CXCL10, and CXCL11 and their ligands, CXCR3, on activating T cells[13,14]; serum levels of indolamine 2,3-dioxygenase activity[15]; transcription factors, T-bet, Fas ligand receptor, and costimulatory CD152 molecule[16]; serum levels of pretransplant interleukin-12 and interleukin-10[17]; urine mRNA of perforin, granzyme, and Fas ligand[18]; and serum levels of soluble CD30 and CD44.[19]

Concerning the treatment, sucbclinical ACR should be considered as well as clinical ACR. Subclinical rejection describes a morphologic pattern of ACR that may occur in up to 30% of the patients without clinical signs and symptoms of rejection that are diagnosed with protocol biopsy. There are studies that suggest these cases should be treated as clinical ACR.[20] Treatment of ACR includes pulse steroid therapy (methyl prednisolone, 125 mg to 1000 mg, for 3 to 5 days) which can reverse 75% of the first rejection episodes. It can be repeated for recurrent or resistant rejections. Thymoglobulin and OKT3 are used as the second line of treatment for steroid-resistant ACR and for Banff type IIB AR or greater; with refractory rejection, a second course can be administered in selected patients with 40% to 50% success of long term graft function. Changing the maintenance

agents from cyclosporine to tacrolimus or adding mycophenolate mofetil or sirolimus may also be effective. Recurrent rejections,[21] ARs with potent immunosuppressive drugs, ARs beyond 6 months posttransplantation, and resistance to therapy are poor prognosis signs and portend poor graft outcome.[22]

REFERENCES

1. Djamali A, Samaniego M, Muth B, et al. Medical care of kidney transplant recipients after the first posttransplant year. Clin J Am Soc Nephrol. 2006;1:623-40.
2. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med. 2000;342:605-12.
3. Almond PS, Matas A, Gillingham K, et al. Risk factors for chronic rejection in renal allograft recipients. Transplantation. 1993;55:752-6.
4. Chertow GM, Milford EL, Mackenzie HS, Brenner BM. Antigen-independent determinants of cadaveric kidney transplant failure. JAMA. 1996;276:1732-6.
5. Abbott KC, Swanson SJ, Richter ER, et al. Late urinary tract infection after renal transplantation in the United States. Am J Kidney Dis. 2004;44:353-62.
6. Denton MD, Geehan CS, Alexander SI, Sayegh MH, Briscoe DM. Endothelial cells modify the costimulatory capacity of transmigrating leukocytes and promote CD28-mediated CD4(+) T cell alloactivation. J Exp Med. 1999;190:555-66.
7. D'Elios MM, Josien R, Manghetti M, et al. Predominant Th1 cell infiltration in acute rejection episodes of human kidney grafts. Kidney Int. 1997;51:1876-84.
8. Segerer S, Cui Y, Eitner F, et al. Expression of chemokines and chemokine receptors during human renal transplant rejection. Am J Kidney Dis. 2001;37:518-31.
9. Zhang PL, Malek SK, Prichard JW, et al. Acute cellular rejection predominated by monocytes is a severe form of rejection in human renal recipients with or without Campath-1H (alemtuzumab) induction therapy. Am J Transplant. 2005;5:604-7.
10. Mauiyyedi S, Crespo M, Collins AB, et al. Acute humoral rejection in kidney transplantation: II. Morphology, immunopathology, and pathologic classification. J Am Soc Nephrol. 2002;13:779-87.
11. Crespo M, Pascual M, Tolkoff-Rubin N, et al. Acute humoral rejection in renal allograft recipients: I. Incidence, serology and clinical characteristics. Transplantation. 2001;71:652-8.
12. Hippen BE, DeMattos A, Cook WJ, Kew CE 2nd, Gaston RS. Association of CD20+ infiltrates with poorer clinical outcomes in acute cellular rejection of renal allografts. Am J Transplant. 2005;5:2248-52.
13. Hu H, Aizenstein BD, Puchalski A, Burmania JA, Hamawy MM, Knechtle SJ. Elevation of CXCR3-binding chemokines in urine indicates acute renal-allograft dysfunction. Am J Transplant. 2004;4:432-7.
14. Abdi R, Tran TB, Sahagun-Ruiz A, et al. Chemokine receptor polymorphism and risk of acute rejection in human renal transplantation. J Am Soc Nephrol. 2002;13:754-8.
15. Friedrich R. Novel biomarkers of allograft rejection: 'omics' approaches start to deliver. Curr Opin Organ Transplant. 2005;10:295-300.
16. Galante NZ, Camara NO, Kallas EG, Salomao R, Pacheco-Silva A, Medina-Pestana JO. Noninvasive immune monitoring assessed by flow cytometry and real time RT-PCR in urine of renal transplantation recipients. Transpl Immunol. 2006;16:73-80.
17. Fitzgerald JT, Johnson JR, Perez RV. Pre-transplant elevations of interleukin-12 and interleukin-10 are associated with acute rejection after renal transplantation. Clin Transplant. 2004;18:434-9.
18. Yannaraki M, Rebibou JM, Ducloux D, et al. Urinary cytotoxic molecular markers for a noninvasive diagnosis in acute renal transplant rejection. Transpl Int. 2006;19:759-68.
19. Ayed K, Abdallah TB, Bardi R, Abderrahim E, Kheder A. Plasma levels of soluble CD30 in kidney graft recipients as predictors of acute allograft rejection. Transplant Proc. 2006;38:2300-2.
20. Nankivell BJ, Chapman JR. The significance of subclinical rejection and the value of protocol biopsies. Am J Transplant. 2006;6:2006-12.
21. Meier-Kriesche HU, Ojo AO, Hanson JA, et al. Increased impact of acute rejection on chronic allograft failure in recent era. Transplantation. 2000;70:1098-100.
22. Leggat JE Jr, Ojo AO, Leichtman AB, et al. Long-term renal allograft survival: prognostic implication of the timing of acute rejection episodes. Transplantation. 1997;63:1268-72.

Correspondence to:
Mohammad-Reza Ganji, MD
Department of Nephrology, Shariati Hospital, Jalal-e-Al-e-Ahmad Hwy, Tehran, Iran
Tel: +98 21 8883 3769
Fax: +98 21 8884 3348
E-mail: mreza@ganji.ir

Received May 2007
Revised August 2007