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Late acute rejection in long-term renal allograft recipients : response to corticosteroid therapy

KEYWORDS: Renal transplantation, Late acute rejection, Histology, Treatment, Prognoses

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ABSTRACT *Objective: The purpose of this stusy was to investigate clinical profile and course and outcome of late acute rejection episodes in cadaveric donor renal allograft recipients. Methods: We prospectively monitored clinical data and renal function at monthly intervals in 440 patients who had received renal allograft transplants at our institution. All had functioning allograft for 1 year or longer. Eighty-three cases of late acute rejection in our center have been clinically observed and analyzed in this study. Results: During a mean follow-up period of 43.6(range 13-64) months,83 patients(18.9%) developed late acute rejections. Of these 83 late acute rejections, as many as 87.9% showed a respone to antirejection therapy with high-dose steroids:23(27.7%) a complete respone and 50(60.2%) a partial response. The response rate was 100% if it was the first acute rejection(35.2% complete and 64.8% partial),81.0%, if it was the second (19.1% complete and 61.9% partial),and no or only a partial response to treatment if it was the third acute rejection episode. Following antirejection therapy,17 of acute cellular rejection (54.8%) were reversed completely,a partial response was obtained in 14(45.2%). Forty-tow patients showed histological features of acute cellular rejection plus chronic rejection. Of these,6(14.3%) were reversed with antirejection therapy, a partial response was obtained in 34(81.0%),and no response in 2(4.8%).Ten rejection showed histological evidence of chronic rejection. Of these, only 2(20.0%) had responded partially to antirejection therapy;8(80%) did not respond.On long-term follow-up, patients who had responseed to antirejection treatment had a significantly better graft survival as compared with non-responding patients:72.0 and 23.0%, respectively. Conclusion: Renal histology provides valuable diagnostic and prognostic information in the management of patients with late allograft rejection. The chances of a response to antirejection therapy are higher during the first episode of late acute transplant rejection as compared with a second or a third late rejection event.*

INTRODUCTION

With development of immunosuppressant, especially appearance and application of new powerful immunosuppressant, early acute rejection has essentially been controlled[1]. However, after one year renal transplantation there are still possibilities of acute rejection episodes(late acute rejection,LAR)[2,3], which may also result in the renal allograft loss[4,5]. However, little is known about late acute rejection including factors affecting its occurrence, its pathology and long-term outcome. Eighty-three cases of late acute rejection in our center have been clinically observed and analyzed. In this study, we investigate the clinical-pathological mechanism, anti-rejection therapeutic effect and its prognoses.

MATERIALS AND METHODS

Patients

Four hundred and ninety-four patients received a cadaveric renal allograft at our unit,among whom 440 cases (89.1%) survived for at least 1 year with normal renal functions. All the patients were followed up with out-patient service once a week for 3 months after the operation, and after that once a month. Through monthly routine observation and monitoring, there were 83 cases stricken by acute rejection episodes one year after renal transplantation. They were 61 males and 22 females with mean age of 37.2±10.6 (18-64) years. The period of acute rejection occurrence was 29.3 (13-90) months.

Immunosuppressive regimen

Monoclonal antibody immunosuppressive induction (preoperative intravenous Basiliximab,20 mg) was performed before surgery. Then, all patients were given an immunosuppressive "old triple-mate regimen" consisting of corticosteroids, mycophenolate mofetil (MMF) and cyclosporine A(CsA). Glucocorticoid treatment started from the beginning of surgery with administration of an intravenous infusion (250 mL) of saline and methylprednisolone (MP, 0.5 g) until arteriovenous anastomosis was completed. MP was then infused intravenously (0.5 g/day) on 1 and 2 days after surgery. On day 3 after surgery, oral prednisone (80 mg/day) was given, and the dose was tapered by 10 mg per day until it was 20 mg/day; This dose was maintained for 3 months, then reduced to 17.5 mg/day and maintained at that level for six months; the dose was then reduced to 10 mg/day and maintained at that level for 1 year. CsA, with the average dosage of 4-5mg/Kg/d. The CsA dosage was regulated with the target plasma trough concentration (100-200ug/L); The initial daily dose of oral MMF was 1.5 g in 2 divided doses. The first dose was within 72 h after surgery, when patients were able to start eating.

Diagnosis of late acute rejection

Diagnostic criteria of late acute rejection include[5,6]: Ⅰ.One year after renal transplantation, blood creatinine level rose progressively or blood creatinine rose 30% more than the original creatinine level; Ⅱ.Meanwhile, renal dysfunction caused by other reasons was excluded, such as hypovolemia, drug-induced renal acidosis and urinary tract obstruction; Ⅲ.The acute rejections must be diagnosed through renal biopsies (Banff Classification Scheme) [7].

Classification of late acute rejections

Clinical classification based on whether there are syndromes in clinic, it could be divided into symptomatic rejection, such as fever, oliguria, proteinuria, edema, hypertension and distending pain in renal allograft, and asymptomatic rejection which has no clinical symptom.

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Pathological classification
Acute cellular rejection(ACR) [6,8]: Tubulitis and/or diffuse interstitial inflammation, mainly mononuclear (small and large amount of lymphocyte, plasmocyte, eosinophil, occasionally neutrophils), accompanied by interstitial edema or bleeding, endothelial cell inflammation; ACR plus chronic rejection (CR) [9,10]: Besides renal interstitial edema and renal tubule pathological changes, the pathologies showed different degrees of interstitial fibrosis, glomerular sclerosis and intimal hyperplasia would appear pathologically; CR[9,10]: Extensive renal interstitial fibrosis, renal tubular atrophy, glomerular hyaline degeneration, mild vascular obstruction and few infiltrating cells.

Treatment of late acute rejection
Anti-rejection and intensive treatment regimen: methylprednisolone(MP) 1.0g/day for 3 consecutive days; then CsA could be replaced by tacrolimus (FK506)(new triple-mate:FK506+MMF+Pred) [11]. The maintenance dosages of FK506 are 0.15mg/Kg/d .

Efficacy evaluation[12,13]
Ⅰ. Complete remission: One month after the anti-rejection treatment, blood creatinine level would reduce to the level before the rejection or the normal level (Scr<130.0umol/L); Ⅱ.Partial remission: One month after the anti-rejection treatment, blood creatinine level would reduce, but not as low as the original level; Ⅲ.No response: One month after the anti-rejection treatment, blood creatinine level did not change or progressively rise. Prognosis of late acute rejection could be assessed by whether the case survives or dies, and whether he returns to have dialysis.

Statistical analysis
The results were shown with mean ± standard deviation. Measurement data incidence or reversal data comparison was tested by t. P<0.05 showed that there was significantly different statistics.

RESULTS
Incidence of late acute rejections
The follow-up was taken for 43.6 monthly (13-64 month) averagely. About the yearly cases, cases of late acute rejection and the incidence of the follow-up period(Table 1). The incidence of late acute rejection was 18.9%. Late acute rejection varied greatly during 1-2 years and 3-4 years after the operation, which was 12.3% to 2.3%. There were 54 cases (65.1%) had the rejections for the first time, 21 cases (25.3%) for the second time, and 8 cases (9.6%) for the third time. 6 cases (7.2%) reduced or stop taking immunosuppressive drugs arbitrarily one year after renal transplantation, resulting in acute rejection due to the lack of immunosuppression.

Clinical characteristics of late acute rejection
Among the 83 cases of late acute rejection, symptomatic rejection and asymptomatic rejection were respectively 47 cases and 36 cases, which covered 56.6% and 43.4% respectively. Symptomatic rejection patients with hypertension were mostly common(61.7%); the cases with edema were 26 (55.3%), cases with proteinuria were 21 (44.7%) with oliguria, 18 (38.3%) gained weight, and only 6 (12.8%) got fever. However, late acute rejection always lacked the typical clinical symptoms of early acute rejection. For example, distending pain and swelling in renal allograft were rarely seen.

After treatment with plus-dose therapy of MP, 87.9% of late acute rejection could be remitted, among which 23 cases (27.7%) were completely remitted, 50 cases (60.2%) were partially remitted and 10 cases (12.1%) were without responses. The treatment effect of patients with acute rejection for the first time was much better than those for the second or third times(Table 2.). The therapeutic effect of patients with acute rejection for the first time: 35.2% were completely remitted and 64.8% partially remitted; the response rate of patients with acute rejection for the second time was 81.0%; While for patients with acute rejection for the third time non-responders were up to 75.0%.

Histopathology of late acute rejection
According to the classification of renal histopathology, all patients of ACR group could get relieved after treatment with plus-dose therapy, among which 17 cases (54.8%) were completed reversed and 14 cases (45.2%) were partially resolved; 6 cases (14.3%) of ACR+CR group were reversed after anti-rejection, 34 cases (81.0%) partially resolved and 2 cases (4.8%) with no response; 2 cases (20.0%) of CR group were partially resolved and 8 cases (80.0%) were without any response.

Incidence of late acute rejection of different immunosuppressive regimen

The incidence (58/248) of late acute rejection of the immunosuppressive regimen adopting "old triple-mate" was obviously higher than that (31/192) of the scheme adopting "new triple-mate", which were 23.4% and 16.1% respectively. The treatment response rate of the treatment group (12/23) replacing CsA into FK 506 was obviously higher than that of the group replacing Aza into MMF, which were respectively 52.2% and 42.0%.

Prognosis of late acute rejection
During the follow-up period, 68 cases survived with the allograft(81.9%). 31 cases in ACR group survived normally, among which 29 cases functioned well with the allograft, with recent Scr<130.0 umol/L, and 2 cases with abnormal renal functions, with Scr respectively 176.0 umol/L and 440.0umol/L; there were 37 cases surviving in ACR+CR group and CR group with the allograft, 12 cases went back to have dialysis because the renal allograft dysfunction had to be removed, and 3 cases died from pulmonary cytomegalovirus infection. The survival rate of remission group treated by anti-rejection was obviously higher than that of the non-response group, which was 72.0% and 23.0% respectively.

DISCUSSIONS
Even though the allogafted kidney was transplanted successfully for many years, acute rejection may also ccurred resulting in graft loss [5,14,15]. It was shown in this study that the incidence of late acute rejection was 18.9%. However late acute rejection varied greatly during the periods of 1-2 years and 3-4 years after the renal transplantation, which was 12.3% to 2.3%. Since some rejections were asymptomatic rejection (43.4%), they were easily to be misdiagnosed even though the renal functions were detected normally and regularly. Clinically the MP pulse-dose therapy often brings severe injuries to the patients. Late acute rejection would cause allograft failure easily, mostly because the clinical symptoms are atypical, or there is no symptom (i.e. subclinical rejection), or because it is only manifested as "borderline changes" histologically [16,17]. Renal allograft biopsy is the most reliable method to diagnose late acute rejection. During the late period of renal transplantation, patients whose allografted functions drop should do further examination to see whether there are

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other potential affecting factors. Once it is doubted that there was acute rejection, renal allograft biopsy must be taken immediately. Recently, some scholars suggest long-term follow-up should be given to renal transplant recipients. Even the recipients whose grafted renal functions are stable should get biopsy regularly [18]. There are obvious differences between late acute rejection and early acute rejection in clinicalopathology, therapeutic effect and prognoses.

Clinical manifestations of late acute rejection are different from those of early acute rejections[8]. Clinical symptoms of early acute rejections are seldom seen, such as pain and swelling of transplanted kidney. It is even only manifested as slow rise of blood creatinine, not eruptive attack (rapid rise of blood creatinine) as in early acute rejection. Once massive proteinuria, edema and hypertension appear, there is possibility of chronic rejection. Pathologically, besides acute cellular rejection with "tubulitis" as the main manifestation, different degrees of chronic changes and rejections often appear. So, late acute rejection accompanied by chronic changes and chronic rejections is the key to predict long-term survival of the renal allograft.

Though the success of curing late acute rejection is not as high as that of early acute rejection, there are still disputes about whether to adopt MP intensive treatment[19,20]. Through clinical and histologic observation of the cases, rather satisfactory efficacy could be gained to have anti-rejection treatment to late acute rejection recipients. It is powerless to try to avoid irreversible loss of transplanted kidney by increasing CsA dosage, which in turn may increase toxic and adverse effects of CsA and advance graft dysfunction[21]. Of these 83 patients with late acute rejections, as many as 87.9% showed a response to anti-rejection therapy with plus-dose steroids (27.7% a complete remission and 60.2% a partial remission). There was no or only a partial remission to treatment if it was the third acute rejection episode (up to 75%). The pathological changes of such recipients were mainly chronic changes, or chronic acute rejection. In our opinion early intensive treatment should be given to late acute rejections together with corresponding follow-up care, such as, to replace CsA into FK506 or MMF into Aza, the response rate of which were 52.2% and 42.0% respectively, for it could effectively prevent and treat late acute rejection and save graft function. However, great caution must be taken to treat recipients with infection. For those with massive proteinuria, high blood pressure and blood creatinine level >400.0 umol/L, or those with mainly chronic changes,is likely to be late humoral rejection or DSA positive rejection [22,23],treatment efficacies of MP pulse-dose were poor, and even severe infection may occur, so intensive treatment is not suitable for them.

In conclusion, different kind of late acute rejections have different intensive treatment prognoses. Complete remission rate of late acute cellular rejection was 54.8%; partial remission rate was 45.2% with good prognoses. Contrarily, all ACR+CR and CR recipients who had no response to anti-rejection treatment back to have dialysis. The chances of a response to antirejection therapy are higher during the first episode of late acute transplant rejection as compared with a second or a third late rejection event. The survival rate of remission group treated by anti-rejection was obviously higher than that of the non-response group, which was 72.0% and 23.0% respectively.

Table 1.Incidence of acute allograft rejection during the late posttransplant period (1 year and beyond)

Follow-up Period (Years)	Patients at risk	Patients developing acute rejections	Incidence(%)
1-2	440	54	12.3
2-3	420	10	2.4
3-4	391	9	2.3
4-5	361	10	2.8
Total		83	

Table 2. Response of late acute rejections to antirejection treatment according to their number of occurrence

Number of late acute rejection	Complete response		Partial response		No response	
	n	%	n	%	n	%
1 (n=54)	19	35.2	35	64.8	0	0
2 (n=21)	4	19.1	13	61.9	4	19.1
3 (n= 8)	0	0	2	25.0	6	75.0

Table 3 Outcome of antirejection therapy in patients with difference histology of late acute allograft rejection

Histologic types	Complete response		Partial response		No response	
	n	%	n	%	n	%
ACR* (n=31)	17	54.8	14	45.2	0	0
ACR+CR (n=42)	6	14.3	34	81.0	2	4.8
CR** (n=10)	0	0	2	20.0	8	80.0

*ACR: acute cellular rejection, **CR: chronic rejection

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