Pathological findings and clinical analyses on delayed renal graft function

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To uncover the pathological feature of delayed renal graft function (DGF) and to explore corresponding prevention and treatments, 84 recipients receiving renal biopsy in our center from December 2007 to September 2010 were enrolled in this study, and 32 cases belonged to DGF. B-type ultrasonography-guided renal needle biopsy with BARD (a company in USA) biopsy needle was performed. After H and E staining, histochemical staining and C4d immunohistochemical staining, pathological types of all biopsy specimens were identified based on Banff'05 standard. DGF was finally confirmed based on the pathologic state of renal graft, and meanwhile clinical data, treatments and curative effects of each patient were recorded and analyzed. After renal biopsy, all patients must be in supine position for 8 h, and anti-inflammatory treatment and hematischesis was given. The main cause of DGF was acute tubular necrosis (ATN) in 20 cases, acute rejection (AR) in 8 cases and nephrotoxicity of immunosuppressants in 4 cases, 31 cases received hemodialysis, and one case received surgical removal. After timely treatments, renal function gradually restored normal in 28 cases, serum creatinine was between 135 to 300 µmol/L in 3 cases, and renal graft was finally removed in one case due to AR. DGF is a common postoperative complication of kidney transplantation, with high incidence. ATN and AR are the main etiological factors of DGF. The appropriate style and timely performance of plasma exchange is crucial for the prognosis of DGF. Other complementary treatments are also conducive to the restoration of renal function. The majority of DGF can gradually recover by plasma exchange in combination with complementary treatments.

Key words: Kidney transplantation, delayed renal graft function, rejection, immunosuppressants, dialysis.

INTRODUCTION

Delayed renal graft function (DGF) is a common postoperative complication of kidney transplantation, with an incidence of 20 to 50% in cadaveric renal transplantation and 4 to 10% in living renal transplantation (Randhawa et al., 2010; Jirasiritham et al., 2010). Early diagnosis and timely and appropriate treatments are crucial for the successful recovery of renal graft function. Renal needle biopsy of renal graft can acquire the level of renal blood perfusion. We retrospectively analyzed 84 cases receiving renal needle biopsy in the past 3 years, and the incidence of DGF was 38.1% (32 cases), in order to analyze the significance of renal needle biopsy of renal graft on the treatment and prognosis of DGF.

MATERIALS AND METHODS

Patients

84 Recipients receiving allograft renal transplantation and renal biopsy in our center from December 2007 to September 2010 were retrospectively analyzed in this study, including 57 males and 27
females, with a mean age of 39.3 years (25~60 years). The indications of renal needle biopsy were serum creatinine increase, hypourcincia, harden texture of renal graft, and ultrasonography revealed the increase of renal vascular resistance after kidney transplantation. Immunosuppressive program of recipients was as follows: 10 mg/kg methylprednisolone intravenously infused during operation, and then the dosage of methylprednisolone was gradually decreased to oral dosage of 8 mg/d; 2 g/d mycophenolate mofetil was orally taken from second day after kidney transplantation; Cyclosporine or FK506 was orally taken from serum creatinine $< 300 \mu\text{mol/L}$. Before renal needle biopsy, bleeding time, clotting time, platelet count, hepatic and renal function was determined, and renal graft must be determined by ultrasonography. The necessity and risk of renal needle biopsy were told to recipients and their family members, and informed consent was obtained from each recipient.

Renal needle biopsy of renal graft

Patients were in supine position, under the guide of color Doppler ultrasound, blood vessels and renal pelvis were avoided, and inferior pole of kidney was obliquely punctured with BARD biopsy needle (USA). The depth of needling was about 2.2 cm usually, two times of puncture was performed at two different sites. After needle biopsy, the puncture site was locally covered and appropriately compressed with pressure dressing, and the patients must be in supine position for less than 8 h, and hemostasis and anti-infection treatment were given. Meanwhile, blood pressure, heart rate, urine output, urine color and other signs were closely monitored.

Pathological examinations

Graft biopsy specimens were immediately immersed in formaldehyde solution and then carefully identified whether it was renal tissues or perirenal fat or other tissue. In order to improve the success rate of renal needle biopsy, another renal needle biopsy at different puncture site was performed if necessary. Pathological examinations of biopsy specimens were immediately performed, including paraffin embedding, sections, HE staining, PAS staining, Masson staining, c4d immunohistochemical staining, and pathological changes under a light microscope. In specimens with suspected rejection, pathological type was identified based on Banff'05 standard (Jirasiritham et al., 2010), and c4d immunohistochemical staining was also performed. Based on the pathological diagnoses, corresponding treatments were given and curative effects were observed. The pathological diagnosis was performed by two experienced pathologists independently and they achieved consensus.

Plasma exchange program

In this study, all DGF patients usually received intermittent hemodialysis (IHD) in 2 to 3 times a week. If vital signs were unstable or there were low blood pressure, severe heart failure or other organ failure in the early stage after kidney transplantation, continuous renal replacement therapy (CRRT) or hemodiafiltration (HDF) should be chosen firstly. In this study, a total of 30 patients once received CRRT or HDF. Besides, one patient received plasma exchange (PE) for 2~5 times due to severe AR.

Adjuvant treatment

Except conventional IHD treatment, the following treatments were also given to promote rapid function recovery of renal graft: (1) Stable mean arterial pressure was maintained to ensure good blood perfusion of renal graft; (2) A low dose of calcineurin inhibitors (3 to 4 mg/kg) and biological immunosuppression was conducive to the recovery of DGF and the decrease of rejection; (3) Application of vasodilators and drug for invigorating blood circulation and eliminating stasis; (4) Sufficient water in body was maintained to prevent cell from dehydration due to frequent dialysis, leading to prolongation of oliguria stage; (5) When there was urine in recipients, furosemide was used to promote the rapid coming of polyuria stage; (6) The changes of panel reactive antibody (PRA) were closely monitored, and anti-rejection treatment or plasma exchange should be given as soon as possible in patients with increase trend of PRA; (7) Systemic support treatment was also given.

RESULTS

Pathological examinations of 32 DGF patients including 21 males and 11 females with a mean age of 35.3 years, 25~60 years revealed ATN in 20 cases (Figures 1 and 2),
nephrotoxicity of immunosuppressants in 4 cases (Figures 3 and 4), and AR in 8 cases (Figure 4), including one case of hyperacute rejection, 6 cases of T cell-mediated AR and one case of antibody-mediated AR of 32 DGF patients, renal function gradually restored to normal level in 28 cases (87.5%) after hemodialysis and adjuvant treatment, and serum creatinine was between 135 to 300 µmol/L in 3 cases (9.4%) within 3 months after kidney transplantation, and renal graft was finally removed in one case due to AR.

DISCUSSION

Within one week after kidney transplantation, serum creatinine decreases for less than 10% of the previous day for continuous 3 days is defined as DGF (Huig et al., 2001). A variety of etiological factors can result in hypofunction of renal graft or even loss, such as rejection (antibody mediate, T cell mediate), DGF, (poly virus and cytomegalovirus) infection, immunodepressive toxic, etc. DGF after kidney transplantation is very common, with an incidence of 10~60%. However, the etiology of DGF is still unknown. Renal biopsy revealed that there was AR in 30% DGF patients at one week after kidney transplantation (De et al., 2006). There was rejection in 18% recipients receiving dialysis at the early stage after kidney transplantation (Sureshkumar et al., 2007). Because the clinical symptoms of rejection are often obscured by the complications of hemodialysis, the concomitant rejection of DGF patients is easily neglected. However, renal biopsy can provide sufficient information to diagnose the rejection in DGF patients (Sulikowski et al., 2010). Humoral rejection is a complicate immune response of host targeting on transplantation antigen of donors, which eventually results in the gradual loss of graft function (Colvin, 2009). In this study, the main etiological factor of DGF after transplantation was ATN,
and it might result from excessive control of liquid, insufficient blood supply, inappropriate preservation of renal graft and so on. Besides, postoperative rejection was also one etiological factor of DGF.

In this study, there were 8 cases of rejection, including typical clinical manifestations of rejection such as fever and gas pains at renal region in 6 cases. There were only the prolongation of oliguria and anuria stage, and renal biopsy revealed that there was slight inflammatory cell infiltration in the interstitial substance of renal graft. AR in the early stage after transplantation might be correlated with repeated transplantation, HLA locus mismatch, recipients of PRA high-sensitivity and ischemia-reperfusion injury of renal graft (Moreira et al., 2011; Bacchi et al., 2010). Therefore, tissue matching of recipients and donors must be identified before transplantation, sensitizing antibody of PRA high-sensitivity recipients must be removed by plasma exchange or immunoadsorption and PRA within normal limits before transplantation could decrease the incidence of AR. Besides, good surgical techniques and skills can ensure successful vascular anastomosis and prevent from stenosis and distort of blood vessels and ureter stoma. It shall be avoided that blood flow is repeatedly blocked. Complete hemostasis can prevent from the hemostasis of hematoma. For DGF resulting from nephrotoxicity of immunosuppressant, the dosage of immunosuppressant shall be decreased, adjunctive therapy and systematic supportive treatments shall be given in time. Because of ischemia-reperfusion injury of renal graft, it is impossible to completely avoid DGF after kidney transplantation. But, all kinds of risk factors of DGF can be removed after transplantation. Recent studies reveal the incidence of DGF may be correlated with donors with age>50 years, preoperative high blood pressure and high serum creatinine, as well as cold ischemia time of graft > 24 h (Collins et al., 1999).

In our center, the age of donors should be less than 40 years old, and there were no history of hypertension and elevated serum creatinine, and removal and preservation of renal graft strictly referred to international standardization process, and cold ischemia time of renal graft was less than 10 h. Therefore, these impacting factors were completely ruled out in this study. In this study, there was no significant difference in the incidence of DGF between female and male recipients. However, previous study showed that there was a higher incidence of DGF in male transplantation (Regele et al., 2001), and the author believed that it might be result from sclerosis of blood vessels due to the more usage of nicotine in male recipients. Recipients with obvious atherosclerosis were excluded in this study; the impact of atherosclerosis on DGF could be neglected in this study. It has been confirmed that high level of PRA is a risk factor of DGF (Narayanan et al., 2010), and the incidence of DGF is significantly increased when PRA > 75% (Colvin, 2009). Preoperative immunological screening and preparation can exclude the impact of high sensitivity recipients on DGF. Thus, many impacting factors of DGF were removed in this study, and we mainly studied the correlation of DGF with blood volume or urine volume of recipients. Nevertheless, renal needle biopsy is a relatively simple diagnostic method with high success rate and safety.

In clinical practice, renal biopsy is usually performed in a majority of patients only when there are clinical manifestations, and thus it is not conducive to the early diagnosis of DGF. However, due to no sufficient positive indications, invasive examinations, complications and cost of renal biopsy, a majority of recipients refuse renal biopsy. Nevertheless, renal needle biopsy is currently one of best examination methods before there is a better diagnostic method. DGF is a common postoperative complication of renal transplantation, with a higher incidence. ATN and AR are the main etiological factors of DGF. The appropriate style and timely performance of
plasma exchange is crucial for the prognosis of DGF. Other complementary treatments are also conducive to the restoration of renal function. The majority of DGF can gradually recover by plasma exchange in combination with complementary treatments. In our opinion, it is more important to prevent DGF. Our experience is that: (1) A good HLA matching is important, and the higher the PRA, plasma exchange and ATG induction therapy could be implemented in high PRA patients. (2) Blood transfusion for uremic patients should be avoided, and erythropoietin can be a application to reduce the allergenic opportunities; (3) In situ perfusion could be used to make the kidney, and renal technology to improved in order to reduce warm ischemia time and cold ischemia time; (4) Surgical skills should be improved to reduce the incidence of surgical complications; (5) Immunosuppressive drugs should be used rationally to prevent its renal toxicity.

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REFERENCES


