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# Delayed Graft Function 5 Months After Living Donor Kidney Transplantation

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
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**Conflict of interest:** None declared

**Patient:** Female, 59  
**Final Diagnosis:** Delayed kidney graft function  
**Symptoms:** —  
**Medication:** —  
**Clinical Procedure:** Living donor kidney transplantation  
**Specialty:** Transplantology

**Objective:** Unusual clinical course  
**Background:** Delayed graft function is a clinical term to describe the failure of the transplanted kidney to function immediately after transplantation.  
**Case Report:** A 59-year-old woman suffered from a rare case of delayed graft function lasting 148 days after unrelated living donor kidney transplantation. Until now, 15 years after transplantation, organ function is still good, with serum creatinine levels about 1.4 to 2.0 mg/dl.  
**Conclusions:** Even after prolonged graft dysfunction, good graft function can be achieved.

**MeSH Keywords:** Delayed Graft Function • Kidney Transplantation • Living Donors

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## Background

Delayed graft function (DGF) after living donor kidney transplantation (LDKT) is reported to be between 1.6% and 7.1% [1,2]. This is less frequent than in deceased kidney transplantation (20–60%). Reasons for and consequences of DGF in LDKT are under debate. The main consequence for the patient is long-term dialysis treatment. Regular blood perfusion of the graft and absence of histological signs of rejection require no specific therapy. In cases in which the causes are unclear, a reduction of the dose of nephrotoxic medication may be an option. DGF seldom lasts longer than 4 weeks, but prolonged dialysis treatment of up to 4 months is also reported. The longest published period with DGF and return of graft function after acute tubular necrosis is 131 days [3]. In general, recovery of kidney function after 3 months is completely unexpected; therefore, the immunosuppressive therapy was reduced step by step and finally stopped completely.

Here, we present a rare case of DGF up to 148 days after LDKT.

## Case Report

We present the case of a 59-year-old (at the time of transplantation) female patient (BMI 30.5 kg/m<sup>2</sup>) who had suffered from chronic nephritis with consecutive impairment of renal function since 1998. She decided to undergo LDKT with her blood-compatible 58-year-old husband as the donor; he offered donation after 1 year of hemodialysis. There were no contraindications to living donation. HLA-mismatch was 0–2 – 1 for A-, B-, and DR loci, respectively. Cross-match was examined twice, while preparation of the graft was performed. Examination of B-lymphocytes and monocytes were both negative. The recipient was CMV-positive, while the donor did not show CMV-IgG. LDKT was performed in March 2000.

Immunosuppressive therapy started a few days prior to transplantation, with tacrolimus (TAC) and mycophenolate mofetil (MMF). Preoperatively, 2×250 mg methyl-prednisolone and single-dose antithymocyte globulin (ATG, 1.25 mg/kg<sub>body weight</sub>) were also administered [4]. After a cold ischemic time of approximately 3 hours, a homogenous reperfusion of the graft occurred and the kidney already intraoperatively showed a distinctive diuresis. Ureterocystostomy was protected by a JJ-stent.

Postoperatively, the patient had stable blood pressure. The diuresis was 170 ml/h and serum creatinine level dropped from 4.4 mg/dl to 2.0 mg/dl at the 2<sup>nd</sup> postoperative day (POD). From the 3<sup>rd</sup> POD, diuresis reduced despite sufficient central venous pressure and adequate blood pressure (median blood pressure >80 mmHg). Because the TAC trough level reached 19.4 ng/ml, the creatinine rise (2.2 mg/dl) was considered as nephrotoxicity

and the TAC dosage was reduced trough level orientated (TAC trough level <15 ng/ml). Given a further rising retention parameter during the following days and a decline of the diuresis (minimum 480 ml/day), Doppler ultrasonography was performed. Here, a distinctly higher renal arterial resistive index with a reduced flow of the peripheral (cortical) artery branches was recorded. Neither graft vessel showed any stenosis. An ultrasound-guided core needle biopsy at the 5<sup>th</sup> POD revealed tissue with flattened tubular epithelia as a sign of tubular insufficiency. Signs of interstitial or vascular graft rejection were not observed. Due to clinical parameters, we suspected early rejection. Therefore, ATG (3.5 mg/kg<sub>body weight</sub>/day) was added to the immunosuppressive medication and the TAC dose was adjusted.

Despite increased diuresis quantities (1000 ml/day), a further rise of the creatinine level (7<sup>th</sup> POD: 4.7 mg/dl) and pulmonary congestion were recorded, requiring first dialysis on the same day. On the following day, an ultrasound-guided biopsy showed moderate focal-shaped fluoride interstitial rejection with distinct edema. The ATG-therapy was continued.

Under regular dialysis, the retention parameters were not convincing and diuresis ranged between 550 and 950 ml/day. The control ultrasound-guided biopsy on the 14<sup>th</sup> POD (7<sup>th</sup> day of ATG-treatment) showed only potential partly reversible tubular damage, partially of the calcineurin-inhibitor-associated type. A moderate, focal-shaped rejection, as well as a tubular atrophy and interstitial fibrosis, were recorded. Signs of vascular rejection, glomerular disease, or renal CMV infection were not established.

Doppler ultrasound, magnetic resonance imaging (MRI), and renal scintigraphy of the transplanted kidney showed a significant restriction of the blood perfusion of the peripheral tissue and reduced tubular function. Stenosis or kinking of the graft artery was excluded.

The antibody treatment was administered for 14 days. In spite of dialysis, an increase of the daily urine production (up to 1700 ml) was documented. It was possible to prolong the intervals of the dialysis to twice a week. Because a further creatinine drop was not noted (between 3.0 and 3.5 mg/dl), it was possible to change the immunosuppression from TAC to sirolimus (SRL, level 8–12 ng/ml) in the 5<sup>th</sup> week after transplantation. After 6 weeks the patient was discharged from the hospital under the conditions described above.

Ten weeks after transplantation, the JJ-stent was removed. A further ultrasound-guided kidney biopsy revealed diffuse tubular atrophy, interstitial fibrosis with focal infections, mid-level glomerular scarring, and definite occlusive sclerosis of the larger artery branches. No signs of rejection or a calcineurin effect were detected. According to histological criteria, improvement of graft function was unlikely.

Taking the above results into consideration, MMF and SRL were stopped, and steroids were down-titrated to 5 mg/day, since there was still remaining urinary production of the graft. Creatinine level decreased step by step to <2 mg/dl without any intensified therapy in the next 4 months. The dialysis intervals were prolonged without an increase of the retention parameters. Last dialysis was performed in November 2000, a total of 148 days after LDKT. Under basic immunosuppression with steroid (5 mg/day) and MMF (3×500 mg/day), serum creatinine levels remained between 1.4 and 2.0 mg/dl. Fifteen years after transplantation, the patient is still dialysis-free.

## Discussion

Criteria for DGF after kidney transplantation are not defined clearly, so we found few comparable studies. The older, but still often-used, definition is “requirement for dialysis in the first week after transplantation” [5]. A comprehensive definition for DGF is the “failure of the graft to function properly in the early phase after transplantation” [6]. Accepted risk factors for LDKT included: older donors (>50 years), higher mismatches, genetically unrelated donors, prolonged warm ischemia, high recipient body mass index, pre-transplant dialysis, and transplantation of the right kidney [7–10]. Of these risk factors, pre-transplant dialysis, donor age >50 years, and possible sex mismatch were relevant for DGF in our patient. All other risk factors, especially a significantly different BMI or an extra-long warm ischemia time, may be excluded as causes.

Acute rejection was excluded by early biopsy within risk management. Independent thereof, the patient with DGF remains less able to tolerate full doses of immunosuppressive drugs, therefore increasing the risk of acute rejection [11]. For our patient, the immunosuppressive therapy required adjustment as well. Course examination on the 8<sup>th</sup> POD proved an interstitial rejection. However, ATG was already added to immunosuppression therapy after the first biopsy. The success of the therapy against rejection was verified by a further biopsy. Independent of this rejection, there may have had a negative impact on the duration of the DGF. The meaning of glutathione S-transferase polymorphism in the presented case as the cause of DGF remains theoretical; at the time, the investigations regarding this had just started. Even today, little data is available for the LDKT group [12], and the same applies to ischemia-reperfusion injury. Although this may also occur

in LDKT, it is more frequent and severe in kidneys from deceased donors [13]. Separate from this, the currently accepted risk factors for ischemia-reperfusion injury were not relevant in our case [14].

The significance of DGF in long-term graft function is very controversial. DGF alone without a rejection period showed good long-term graft survival [1].

Nephrotoxic adverse effects of calcineurin inhibitors are well known in kidney transplantation. By replacing TAC with SRL, the potential nephrotoxic immunosuppression was taken into consideration. In 2000 there was little experience in the use of SRL after kidney transplantation, but today SRL is more often used, primarily after organ transplantation. However, some investigations suggest that SRL negatively influences the incidence and duration of DGF [15,16]. Any additional negative influence of SRL in our patient is speculative. Nevertheless, after the convalescence of the graft function, the immunosuppression was carried out as dual therapy with steroids and SRL. The specifications for mTOR inhibitor and DGF mentioned above were not available then; therefore, the least nephrotoxic therapy with a calcineurin-inhibitor-free regimen was carried out.

Retrospectively, it is possible that the core needle biopsy specimens, taken 10 weeks after transplantation, may have shown non-representative kidney tissue; otherwise, recovery of the kidney function would have been impossible. Reduction of immunosuppression nearly 3 months after transplantation with missing graft function was an option under these circumstances. From a retrospective point of view, it was justified.

## Conclusions

It may be assumed that, even after prolonged graft dysfunction, good renal function can be achieved. Ceka and Terasaki reported good graft function (creatinine 1.9 mg/dl) over 13 years after deceased kidney transplantation despite a DGF period up to 90 days [3]. The timeframe of 148 days of DGF duration presented here has to be considered as extraordinary, but with a positive result for the patient.

## Conflict of interest

None declared.

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