Can zero-hour cortical biopsy predict early graft outcomes after living donor renal transplantation?

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Abstract

Introduction: The aim of this study was to identify relevance of subclinical pathological findings in the kidneys of living donors and correlate these with early graft renal function.

Methods: This was a prospective study on 84 living donor kidney transplant recipients over a period of two years. In all the donors, cortical wedge biopsy was taken and sent for assessment of glomerular, mesangial, and tubule status. The graft function of patients with normal histology was compared with those of abnormal histological findings at one, three, and six months, and one year post-surgery.

Results: Most abnormal histological findings were of mild degree. Glomerulosclerosis (GS, 25%), interstitial fibrosis (IF, 13%), acute tubular necrosis (ATN 5%), and focal tubal atrophy (FTA, 5%) were the commonly observed pathological findings in zero-hour biopsies. Only those donors who had histological changes of IF and ATN showed progressive deterioration of renal function at one month, three months, six months, and one year post-transplantation. In donors with other histological changes, no significant effect on graft function was observed.

Conclusions: Zero-hour cortical biopsy gave us an idea of the general status of the donor kidney and presence or absence of subclinical pathological lesions. A mild degree of subclinical and pathological findings on zero-hour biopsy did not affect early graft renal function in living donor kidney transplantation. Zero-hour cortical biopsy could also help in discriminating donor-derived lesions from de novo alterations in the kidney that could happen subsequently.

Introduction

Chronic kidney disease (CKD) is a common and rapidly increasing global public health problem, both in developed and developing countries. Kidney transplantation remains the treatment of choice for end-stage renal disease (ESRD), as it leads to longer survival and superior quality of life.[1] it is estimated that in India, 3500 patients undergo renal transplantation annually.[2]

The graft recipients, their relatives and transplantation team are always eager to know how the grafted kidney will behave and how long will it survive. Several attempts have been made to predict the early graft outcome by assessing the histological changes at "zero-hour" graft biopsy; however, the issue still remains controversial.[3-6] The post-revascularisation zero-hour biopsy of renal allograft could provide useful information on subclinical renal lesions present in the healthy donors and the pathological changes that are being transmitted from the donor to recipient via grafted kidney. It might also act as a baseline biopsy for comparing morphology with subsequent graft biopsies. Lesions like intimal fibrosis, glomerulonephritis, tubular atrophy and interstitial fibrosis, etc. may either pre-exist or may be of new onset. The majority of existing studies reported on zero-hour biopsy predicting early and late graft outcomes have been in cadaveric donors. Information on post-revascularisation renal allograft biopsies in live related donors is limited.

Methods

After getting institutional ethics committee clearance, a prospective study was conducted from March 2014 to December 2016. Informed consent from both the donors and recipients undergoing live donor renal transplantation were obtained.

A total of 84 patients (43 males and 41 females) aged 13–63 years who underwent open donor nephrectomy and renal transplantation at the institution during the above-mentioned period were enrolled in the study. Preoperative donor evaluation was done to evaluate medical, surgical, and psychosocial suitability for living donation prior to selection of patients for transplantation.

All the recipients included in the study were given same standard immunosuppressive therapy regimen consisting of tacrolimus tablets 3 mg once daily (OD), mycophenolate

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mofetil tablets 500 mg OD, and injection methylprednisolone 500 mg intravenously daily starting five days prior to the transplantation. Injection basiliximab 20 mg intravenously in 100 ml normal saline stat was given to all the recipients if the donor was unrelated. Injection methylprednisolone was replaced by prednisolone tablets 30 mg OD from postoperative Day 3.

A cortical wedge biopsy of the size 1x0.5x 0.3 cm^3 of the transplanted kidney was taken immediately after revascularization on completion of vascular anastomosis. The main idea behind taking wedge biopsy was to ensure adequate tissue (at least 20 glomeruli per core) for histopathological examination. In all 84 cases, the wedge biopsy was taken by single transplant surgeon. Specimens were fixed immediately in 10% buffered formalin and embedded in paraffin. Three micron thick serial sections were cut and stained with H&E, periodic acid-Schiff, Masson's trichrome, and periodic Schiff silver methylamine. A detailed histological examination of post-revascularization graft biopsies was performed and looked for the following:

1. Glomerular status, number of glomeruli per core, and any evidence of glomerular sclerosis
2. Mesangial status
3. Tubule status and number of tubules per core

In all transplant recipients, graft function was assessed by serum creatinine (Cr) post-transplantation. All patients had followup visits in their first, third, and sixth month, and one year postoperative periods to determine if there was any allograft dysfunction, defined as serum Cr >15% of the baseline value or lack of response to increasing steroid dose. All the patients who developed delayed graft function had to be supported by hemodialysis post-transplantation until these renal functions normalized. All those patients who needed followup biopsies post-transplantation underwent percutaneous biopsy under computed tomography (CT) guidance and by single expert radiologist.

Statistical analysis

Pearson correlation coefficient test was used for correlating serum Cr values of patients with normal donor histology with serum Cr values of patients who had abnormal donor histology at one month, three months, six months, and one year post-transplantation.

Table 1. Effect of various histological changes on graft function at 1 month

Histological changes if cortical biopsy	Number of patients (out of 84)	Effect on graft function
Normal histology	48 (58%)	No effect
Glomerulosclerosis	21 (25%)	No effect
Interstitial fibrosis	11 (13%)	Delayed graft function: 4
Acute tubular necrosis	4 (5%)	Acute rejection: 2 Delayed graft function: 2
Focal tubal atrophy	4 (5%)	No effect

Results

Of 84 donors, 43 subjects were males and 41 were females. The mean age of the patients was 41±9.5 years.

Forty-four of 84 patients (52%) had normal histology of the donor kidney. Only 40 patients (48%) had abnormal histological changes, which included glomerulosclerosis (GS, 25%),interstitial fibrosis (IF, 13%), acute tubular necrosis (ATN, 5%), and focal tubal atrophy (FTA, 5%) (Table 1).

The effects of various histological changes on graft function at one month are given in Table 1. Only recipients with grafts having IF and ATN showed progressive deterioration of renal function at one month. Out of four patients who had ATN on biopsy, two developed acute rejection and two had delayed graft function post-transplantation. Four patients of the IF group also had delayed graft function. Other histological changes in the graft had no effect on graft function.

Both the patients who had acute rejection died within three months post-transplantation due to systemic infections. All the patients who had delayed graft function required hemodialysis post-surgery for optimization of kidney function.

Table 2 shows serum Cr values in patients with normal histology and also of patients with various coexisting histological changes in donor kidneys preoperatively and at one month, three months, six months, and one year postoperatively. Only IF and ATN showed progressive increase in serum Cr values at one month and one year. In cases of both the histological changes, rise in serum Cr started at one month postoperatively and continued to rise until one year of followup. On correlating serum Cr values of these patients

Table 2. Comparison of serum creatinine in patients with normal histology with that of various coexisting histological changes at 1, 3, 6, and 12 months post-surgery

	Mean serum creatinine levels (mg/dl)				
	Preoperative	1 month	3 months	6 months	12 months
Normal histology	0.80±0.19	0.82±0.18	0.83±0.18	0.83±0.18	0.83±0.19
Glomerulosclerosis	0.83±0.24	0.91±0.23	0.92±0.23	1.05±0.22	0.99±0.22
Interstitial fibrosis	0.87±0.24	1.06±0.22	1.20±0.21	1.40±0.24	1.61±0.28
Acute tubal necrosis	1.05±0.21	1.15±0.21	1.15±0.01	1.25±0.07	1.30±0.01
Focal tubal atrophy	0.65±0.07	0.75±0.07	0.90±0.01	1.00±0.01	1.15±0.07

Table 3. Comparison of p values of normal histology with various coexisting histological changes

	Preoperative	1 month	3 months	6 months	12 months
Normal histology vs. glomerulosclerosis	0.8004	0.6119	0.6192	0.7233	0.0581
Normal histology vs. interstitial fibrosis	0.062	0.017	0.0024	0.0017	0.0009
Normal histology vs. acute tubal necrosis	0.0742	0.002	0.0048	0.0008	0.0003
Normal histology vs. focal tubal atrophy	0.2482	0.390	0.072	0.062	0.083

with those patients who had normal histology (Table 3), both IF and ATN showed strong positive correlation (p=0.0003 and p=0.0009 at one year post-surgery, respectively). Patients with other histological changes in donor biopsy, like GS and FTA, also showed marginal rise in serum Cr obtained post-operatively, which was statistically insignificant (p=0.0581 and p=0.083 at one year, respectively).

Discussion

It is well-known that there are various donor and recipient factors that determine the function and survival of the graft after live donor renal transplantation. Donor-related factors, including age, organ size and quality, preoperative glomerular filtration rate, and comorbid conditions (such as diabetes, hypertension, and smoking), have been reported to have significant bearing on graft function post-transplantation; however the role of zero-hour cortical biopsy taken from donor kidney post-transplantation on graft function postoperatively has not been widely studied. In this case, the cortical wedge biopsy was taken, as it provides adequate quantity of tissue (at least 20 glomeruli per core) needed for histopathological examination.[7] In our study, zero-hour cortical biopsy showed that GS (25%) was the most common histological abnormality, followed by, ATN (5%), IF (13%) and FTA (5%), which is almost similar to the histological findings noted by Lee at al. [8]

A high grade of GS has been reported to be a good predictor of early graft dysfunction;[8] however, in our study, the grade of GS was not taken into account due to the difference in the number of glomeruli per core seen in different biopsy specimens. The presence of IF correlated well with worst results in long-term graft survival (chi-square p=0.029; relative risk 2.23; 95% confidence interval 1.07–4.64). Similar results have been reported by Lopes et al,[9] who found a positive correlation between IF and serum Cr at three and six months, but no correlation with TA and GS. Interestingly, the same authors assumed that none of the histological variables and scores provided perfect predictions and cautioned that results should be interpreted in the context of all available information on donors and recipients.[8,10]

Table 4 shows comparison of our study with the standard published literature in terms of types of histological changes seen, overall survival, number of deaths, and allograft dysfunction; our findings matched the majority of the studies.

It has been reported that Implantation Biopsy Score (IBS) 4–6 could determine an increased risk of early graft loss, especially primary nonfunction.[11] Higher IBS grades predict lower graft function until the third postoperative year; but in this cohort, we could not assess IBS because of shorter followup period.

Currently, preoperative biopsies could be considered as a graft survival prediction tool, with high specificity (despite a low sensitivity). Since the advent of the cyclosporin era of immunosuppression, we have dramatically reduced the impact of allograft acute rejections, remaining with late losses due to chronic allograft dysfunction.[11]

Limitations of the study

The sample size of the study was small; further studies with larger numbers of transplant patients is needed so as to extrapolate the required outcomes representative of the population at large. The effects of preoperative estimated glomerular filtration rate and its correlation to the donor's age and comorbidities, which could have affected graft function post-transplantation, were not studied. Followup of our patients was for a short period and hence long-term effect on graft function could not be assessed.

Conclusion

Zero-hour cortical biopsy provides information about the general status of the donor kidney and presence or absence

Table 4. Comparison of our study with published literature

Various studies	Histological changes seen	Overall survival at 1 year	Allograft dysfunction	Number of deaths
Our study	GS-25%, IF-13%, ATN-5%, FTA-5%	96%	7.4%	2 (3.8%)
Naderi et al (2014)[12]	GS-35%, IF-16%, FTA-6%	94%	9%	3 (5.5%)
Kaplan et al (1975)[10]	GS-23%, IF-6%	98%	15%	1 (3%)
Chamienia et al (2004)[13]	GS-24%, FTA-15%	100%	10%	No deaths
Hashikura et al (2004)[14]	GS-30%, HA-6%	89%	8%	No deaths

ATN: acute tubal necrosis; FTA: focal tubal atrophy; GS: glomerulosclerosis; IF: interstitial fibrosis.

of subclinical pathological lesions; however, it was observed that a mild degree of subclinical, pathological findings on zero-hour biopsy did not affect early graft renal function in living donor kidney transplantation. IF and ATN were the only histological abnormalities associated with significant effect on allograft dysfunction.

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This paper has been peer-reviewed.

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