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More than Twenty Years' Experience with "Zero-Hour" Transplant Kidney Biopsy

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Abstract

"Zero-hour" biopsies of 968 transplant kidney have been performed since 1994. Donor kidneys were categorized into five groups based on the morphological findings in "zero-hour" biopsies. No morphological abnormalities were found in 40.5% of the cases. Arteriosclerosis was seen in 21.3% of donor kidneys. Acute tubular necrosis 27.8%, chronic tubulointerstitial nephritis 3.9% or glomerulonephritis 6.5% were detectable in the cases remained. Not significant differences were found in individual groups concerning basic disease, duration of supplementary kidney treatment prior to transplantation, mean age of recipients and HLA, B and DR mismatches. During the follow-up period (on the average 1764 days) 733 biopsies were performed. Side effect due to the performance of "zero-hour" biopsy was not observed. Massive haematuria resulting bladder tamponade occurred only once during re-biopsies. We found very worse early and long-time results at the chronic tubulointerstitial group. Arteriosclerosis in the transplant kidney is one of the alloantigen independent factors of the chronic allograft nephropathy. "Zero-hour" biopsies could be useful and safe tools to predict early graft function. Additionally, "zero-hour" biopsies help the histological interpretation of consecutive graft re-biopsies.

Keywords: "Zero-Hour" Biopsy; Kidney Transplantation; Chronic Allograft Nephropathy

Abbreviations

AR: Acute Rejection; AS: Arteriosclerosis; ATN: Acute Tubular Necrosis; CAN: Chronic Allograft Nephropathy; DGF: Delayed Graft Function; GN: Glomerulonephritis; HLA: Human Leukocyte Antigen; MAC: Membrane Attack Complex; NVG: Non-Viable Graft; Se: Serum; TIN: Tubulointerstitial Nephritis

Introduction

The growing demand for transplantation resulted in easing kidney donor criteria. As a consequence, the number of marginal donors and non-viable grafts increased [1]. We wanted to answer the question, how much the pathological findings of "zero-hour" biopsy determine the early postoperative period and how much it can be considered as an alloantigen-independent factor in the development of chronic allograft nephropathy in a big patient group.

Conflicting opinions were voiced on its predictive value. Some experts assess it inadequate to determine early graft rejection, early and late graft function while others take into consideration its predictive feature [2,3]. Representatives of different viewpoints agreed that "zero-hour" biopsy may be the basis for comparison in analysis of subsequent rebiopsies [4,5].

Materials and Methods

Between 13 May 1994 and 16May 2017, 968 "zero-hour" biopsies were performed just before transplantation. Grafts came from cadaver donors (2 non-heart beating donors) in 896 cases while in 72 cases grafts were transplanted from living donors. In 125 cases both kidneys of the same donor were transplanted in our clinic. Combined transplantation of the kidney and pancreas was performed in 94 cases. Four patients received the third, 33 patients the second while the others the first transplantation.

"Zero-hour" biopsy was performed from the upper pole of the kidney just before the transplantation after the kidney had been dissected in icy bath. After the wedge biopsy of about a rice size tissue, the wound was closed by atraumatic continuous suture. Histological changes noticed

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Table 1: Contrasting of different type of histological group (bold: significant different to the normal histological group, p<0.001).

	Normal	AS	ATN	TIN	GN
Number of patients/ frequency	392/40.5%	206/21.3%	269/27.8%	38/3.9%	63/6.5%
Age of donor (year)	33.4	54.2	36.1	51.8	45.6
Start of kidney function (day)	0.16	2.2	6.1	4.3	3.2
Number of DGF/frequency	41/10.46%	56/27.18%	126/46.84%	17/43.58%	14/22.22%
Number of NVG/frequency	2/0.05%	6/2.9%	9/3.3 %	2/5.26%	0
Se creatinine after charge (µmol/L)	159.1	260.4	342.9	307.2	214.8
Se creatinine 3 months later (µmol/L)	118.6	203.9	163.5	285.9	170.7
Se creatinine last (µmol/L)	113.4	216.8	118.6	318.7	120.3
Number of acute rejection/ frequency	301/76.8%	181/87.9%	244/90.7%	32/84.2%	49/77.8%
Steroid resistant AR/rate*	21/5.35%/6.97%	19/9.22%/10.49%	27/10.03%/11.06%	7/18.42%/21.87%	4/6.34%/8.16%
Number of CAN/frequency	41/20.15%	90/43.68%	59/21.93%	30/78.95%	14/22.2%
Development of CAN (day)	1186.3	512.8	991.4	228.5	973.8
Return to dialysis/rate	41/10.46%/51.89%	81/39.32% 90%	40/14.87%/67.8%	30/78.95%/100%	10/15.87%/71.43%
Start of Re-dialysis (day)	1158.7	671.9	1336.7	257.4	1329.6
Number of functioning graft/rate	301/76.78%	80/38.83%	188/69.89%	3/7.89%	46/73.01%

*First value show correlate the rate of the percent aged to the all patients of group, the second value to the number of cases above

during process developed either in the donor or during storage. Side effect due to the performance of "zero-hour" biopsy was not observed.

Later, subsequent biopsies were performed when:

- More than 7 days delay occurred in the onset of graft function,
- Clinical suspect of acute rejection a raised,
- Steroid-resistant acute rejection occurred,
- After immunotherapy,
- Serum creatinine increase was not clinically justified.

Morphological analysis of histological sections was performed by light microscope, immunofluorescence microscopy (IgG, IgM, IgA, C3, MAC), transmission electron microscopy according to standard techniques. Banff criteria were essential to determine histological severity [6].

Results

Grafts of donors did not show any macroscopic changes from normal kidney, laboratory findings and vital parameters met the international recommendation/criteria. In spite this fact hardly more than one-third of grafts had normal histological pictures. In the remaining cases Arteriosclerosis (AS), Acute Tubular Necrosis (ATN), Tubulointerstitial Nephritis (TIN) or Glomerulonephritis (GN) were found in the pathological findings.

Not significant differences were found in individual groups concerning basic disease, duration of supplementary kidney treatment prior to transplantation, mean age of recipients and HLA, B and DR mismatches. During the follow-up period (on the average 1764 days) 733 biopsies were performed. Massive haematuria resulting bladder tamponade occurred only once during rebiopsies. In spite of conservative treatment it reoccurred every 3-4 days. With the help of image forming processes the location of bleeding could not be detected so we had no other choice than to remove the graft. Since we changed to ultrasound guided biopsy for histological diagnosis we have not experienced any side effects demanding intervention [7].

Comparable aspects of different groups are summed up in Table 1. Comparison of groups was based on such aspects which had an influence on both the short-, and long-term results and showed significant changes among the groups. The examination of significance was performed by means of t-probe and difference was considered to be significant in case of p<0.001 (IBM SPSS Statistics software -IBM Corporation, Armonk, NY, USA).

Discussion

Normal histological group

Best results can be expected in this group both on short and long term, if serious side effects do not develop during the early postoperative period. The risk of development of severe rejection process is low. When adequate attention is paid to follow up, and patient compliance is satisfactory, the treatment of Chronic Allograft Nephropathy (CAN) detected at early stages can be successful as well as effective graft function period can significantly be improved [8].

Grafts with arteriosclerosis

Aging increases the probability of arteriosclerosis in donors [9]. These grafts are characterised by acceptable early function but later they lack the necessary reserves for long term adequate function [10]. Patients having this kind of kidney form a potential risk group for CAN as the developed histological changes are practically identical with those demonstrated by grafts with arteriosclerosis [11]. Long term function of these grafts can be worsened by prolonged cyclosporine therapy and are negatively influenced by many of chronic renal failure end-stage complications such as hypertension, hyperlipidaemia and diabetes mellitus. In the absence of "zero-hour" biopsy it is difficult to diagnose cyclosporine nephrotoxicity as cyclosporine similarly to arteriolosclerosis forms a nodular picture [12].

Acute tubular necrosis

As graft tubular damage mostly occurs in the same age group where grafts have normal histological pictures [13]. It is to be expected

that these grafts would have belonged to the normal group but during the treatment of the patient, operation, perfusion or storage they suffered damages to a lesser or more extent.

In acute tubular necrosis of grafts the result of "zero-hour" biopsy may predict delayed graft function [14]. These grafts are advisable to be followed by biopsy once a week until the onset of the function. The degree of regeneration can be assessed in this way. In non-functioning grafts due to ATN the development of acute rejection can be more often observed which may remain undiagnosed and untreated in absence of biopsy during the follow-up.

Furthermore, characteristic features are poorer graft survival and function as well as higher rate of nonviable grafts. The need for supportive haemodialysis is the highest in this group [13]. Later no significant differences can be observed in functioning grafts compared to the normal group.

Tubulointerstitial nephritis

In spite of the small number of cases it is obvious that the tubulointerstitial group has the most unfavorable prognosis [16]. They have higher serum creatinine level, elevated acute rejection rate and the highest graft loss rate. The most important characteristics of this group are the poor early and late graft functions. Due to this fact CAN develop significantly earlier and we are helpless in these cases [15]. In spite of our therapeutic efforts we could not achieve essential changes. Prognostically, this group is considered to be the most unfavorable. If histological findings were available before the operation then transplantation of kidneys in this group could be avoided.

Group of glomerulonephritis

IgA nephropathy was the observed lesion in every case, when donor's anamnesis involved alcoholism [17]. Renal function measured before donation proved to be normal. Significant difference from the normal group was only detectable in their mean age. Their functions approached the findings of the group with normal histological results both in a short- and long term. The results of the subsequent re-biopsies were unexpected as the original histological changes were totally eliminated [17]. An interesting aspect of IgA glomerulonephritis is that it causes chronic renal failure then, after the transplantation it may appear in the transplanted graft but at the same time IgA nephropathy in the transplanted graft terminates due to immunosuppression. It is thought-provoking. It does not have a disadvantageous effect on the outcome of the transplantation so no further examinations were carried out in this direction [18].

Conclusion

On the basis of the long-term follow up of 968 kidney or combined kidney and pancreas transplants' we can establish that the findings of "zero-hour" biopsies have an effect on the assess of both the early postoperative period and the subsequent term [5]. They may help in clinical judgment of postoperative anuria, influence therapeutic decisions in case of a severe, acute rejection or they can have a prognostic feature in the development of chronic allograft nephropathy.

With full knowledge of results, those in TIN group, 3.9% out of transplanted grafts should have been disregarded. Not even the possessed outcome or the retrospectively analysed data could prove a parameter which could have served as a basis for selection before donation. The unfavorable outcome of Grade III AS was unforeseen as changes of blood vessels in the kidney were not proportioned with sclerosis of big vessels. It is true that donors in both groups were aged over 50 years or in most of the cases they were defined as marginal donors. One of the main characteristics of marginal grafts is that damages due to ischemia/reperfusion, length of cold ischemia and hemodynamical stability of recipient are highly emphasised. In the light of this fact some principles of the national transplantation program should be revised. In case of marginal donors taking histological sample could be introduced during donation and HLA determination would not be necessary but two blood group compatibles recipients - in good health condition - from the region on the basis of negative cross matching would get the kidneys. On the basis of histological findings, a considerable proportion of non-viable graft could be screened. Ischemic period would be within 8 hours reducing damages due to ischemia/reperfusion. Neglecting marginal donors in transplantation is unfeasible, because of the increasing demand. If we had the chance to increase the supply of donor organs then the severity of the acceptance criteria of marginal donors could be increased [19].

We believe the clinical value of "zero-hour" biopsy is expressed:

1. In the judgment of primary non-functioning grafts.

2. In the influence on treatment strategy for severe rejection processes.

3. In its predictive value in both the short- and long- term results.

4. It could help for the pathologist to evaluate rebiopsies.

5. In determination of effective treatment for chronic allograft nephropathy.

6. In cases of marginal donors the findings of biopsy taken during the donation could be conclusive.

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