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CHRONIC ALLOGRAFT NEPHROPATHY (CAN) IN EARLY RENAL PROTOCOL BIOPSIES: DOES TREATMENT OF BORDERLINE AND SUBCLINICAL ACUTE REJECTIONS PREVENT DEVELOPMENT AND PROGRESSION OF CAN?

J. Masin-Spasovska[1], G. Spasovski[1], M. Polenaković[1], S. Džikova[1], G. Petruševska[2], B. Dimova[2], Lj. Lekovski[3], Z. Popov[3], N. Ivanovski[1]

[1]Department of Nephrology Faculty of Medicine, Skopje, Republic of Macedonia
[2]Department of Pathology Faculty of Medicine, Skopje, Republic of Macedonia
[3]Department of Urology Faculty of Medicine, Skopje, Republic of Macedonia

A b s t r a c t: Histological markers of chronic allograft nephropathy (CAN) in early protocol biopsies may ultimately result in deterioration of graft function. The aim of our study was to evaluate risk factors of early CAN histology and to determine whether treatment of borderline and subclinical acute rejections (BR/SAR) at 1-month postransplant, prevents development and/or progression of CAN at 6-month biopsy.

Thirty-five paired kidney allograft biopsies at 1 and 6 months after transplantation were blindly reviewed using Banff'97 criteria. The mean CAN score (sum of histological markers for chronicity) increased significantly at 6-month biopsy (1.83 ± 1.46 *vs* 4.66 ± 2.35; $p < 0.01$). No CAN was present in 27/70 biopsies (38.6%), 71.4% showed progression and 28.6% were with stable CAN at 6-month biopsy. When compared according to the progression, mean histological index (HI) score (sum of acute/chronic changes) in progressed CAN group (pCAN) increased significantly at 6-month biopsy (5.0 ± 3.0 *vs* 9.5 ± 2.8; $p < 0.001$). At 1-month biopsy, BR/SAR were found in 68% and 70%, in the pCAN and stable (sCAN) groups, respectively. The percentage of treated BR/SAR in sCAN group was significantly higher (57.1 *vs* 23.5%; $p < 0.05$), and the score of acute histological lesions lower (1.08 ± 0.95 *vs* 0.35 ± 0.66; $p < 0.01$) at 6-month biopsy.

In conclusion, 1-month protocol biopsy may be valuable to uncover BR/SAR and the presence of early CAN in stable renal allografts. Progression of CAN at 6-month biopsy in our study was found to be associated with a greater number of

untreated BR/SAR at 1-month biopsy. This observation may have important implications in the design of clinical trials aimed to prevent the progression of CAN.

Key words: kidney transplantation, protocol biopsy, borderline rejection, subclinical acute rejection, chronic allograft nephropathy.

Introduction

Chronic allograft nepropathy (CAN), clinically presented by progressive renal dysfunction and often accompanied by proteinuria and hypertension is the main cause of kidney-transplant failure despite improvements in transplant immunosuppression [1]. Despite well defined histological presentation by chronic interstitial fibrosis, tubular atrophy, vascular occlusive changes, and glomerulosclerosis, the pathophysiology of CAN remains poorly understood. Both, immunologic and nonimmunologic risk factors are associated with the late renal allograft loss in CAN. Nonimmunologic or clinical factors reported to be associated with CAN are: donor age and female sex, donor disease, recipient age and female sex, recipient primary cause of renal disease, body mass index (BMI), proteinuria, calcineurin-inhibitor nephrotoxity, hypertension, hyperlipidemia, hyperglycemia, infections, nephrocalcinosis and others. The immunological mechanisms include: HLA missmatching, ischaemia-reperfusion injury, delayed graft function (DGF), acute rejection episodes, subcinical rejections, inadequate immunosupression, exacerbating pre-existing donor disease, and recurrent or *de novo* glomerulonephritis [2, 4].

There is increasing evidence that CAN progresses rapidly during the first few months after transplantation and slowly thereafter. Several reports suggested that acute rejection episodes and CAN are often "subclinical" without causing a measurable decrease in renal function [5, 6]. A number of studies on protocol biopsies have revealed variable frequencies of subclinical acute rejection (SAR) or borderline rejection (BR) and CAN already in early phases-within the first months after transplantation, in stable allografts [7]. Shapiro *et al*. described a prevalence of BR in 21% and SAR in about 25% of protocol biopsies performed at 1 week after transplantation [8]. Similarly, Rush *et al*. [9] observed BR and SAR in 21 and 33% of stable allograft patients respectively, while in the recent report of Nankivell *et al*. the reported prevalence was 49% and 29%, at 3 months protocol biopsies, respectively. In addition, further analysis of protocol biopsies at 3 months has revealed the prevalence of CAN in 21.6% [10]. Seron *et al*. has reported an even higher prevalence of CAN in about 42% of protocol biopsies performed 3 months after transplantation [11].

There is growing evidence in favour of treating biopsy-proven subclinical acute rejection episodes. Rush *et al*. reported improved allograft outcome after treatment of early SAR (1–3 months) with high-dose steroids, with evidence of a lower rate of early (months 2 and 3) and late (months 7–12) acute

rejection episodes, a reduced chronic tubulointerstitial score at 6 months, and an improved allograft function in treated patients when compared to untreated controls [12, 13]. Additionally, Nickerson *et al*. has reported that an increased baseline immunosuppression and corticosteroid treatment of early SAR was associated with a decrease in late clinical rejection episodes, considered as a marker for a poor graft outcome [14].

Our study aimed to evaluate the risk factors of histological findings of CAN at 1-month biopsy and to determine whether the treatment of borderline and subclinical rejections (BR/SAR) at first month post-transplant, prevents development and/or progression of CAN at 6-month biopsy.

Material and methods

Thirty-five consecutive living related (LR) transplant patients were studied. All patients received their first transplant. Methylprednisolone (500 mg) and Daclizumab (Zenapax; 1 mg/kg BW at implantation and thereafter every 2 weeks x five doses) were administered as induction therapy. Maintenance immunosuppression included: cyclosporine A (Neoral; 6 to 8 mg/kg/day) to reach target C_2 levels (blood concentration 2 hours after administration of the drug), prednisolone (1 mg/kg/day tapered to 0.1 mg/kg/day after 4 weeks) and mycophenolate mofetil (Cellcept 1.5–2 g/day).

During the first postoperative month patients with DGF who underwent post-transplant acute tubular necrosis or experienced a clinical episode of acute rejection (AR) were treated with haemodialysis or pulse corticosteroids, respectively, whenever an increase in serum creatinine >20% or decrease in urine output for 2 consecutive days was observed. These cases were included for biopsy if their graft function was stable (no change in serum creatinine > 20%) for at least 2 weeks before the first biopsy. Patients with histology at 1-month biopsy of BR or SAR (i.e. AR type I or IIA) and an increase in serum creatinine between 10 and 20 % from baseline (serum creatinine 2 weeks prior to the biopsy) were consequently treated with pulse corticosteroid therapy. The patients with a histology of BR or SAR followed by an increase in serum creatinine < 10% from baseline were not treated.

Protocol biopsies were performed using an ultrasound-guided automated biopsy "gun". The formalin fixed biopsies were embedded in paraffin, serially sectioned at 3 to 5 μm thickness and stained with haematoxylin-eosin (HE), periodic acid-Schiff (PAS), Masson's trichrome as well as methenamine silver. Biopsies were considered adequate when they contained $\geq$ 7 glomeruli and at least one artery. Renal lesions were blindly reviewed for evidence of acute and chronic changes by the same pathologist. Descriptive morphologic criteria according to the Banff 97 scoring schema using a scale from 0 to 3 were employed [15]. CAN score was calculated as a sum of scores for the individual histological markers for chronicity: interstitial fibrosis, tubular atrophy, vascular fib-

rous intimal thickening, arterial hyalinosis and chronic glomerulopathy. The histological index (HI) was calculated as a total sum of scores for acute and chronic changes. Patients were classified according to the progression or non-progression of CAN. The progression was defined as an increase in the grade of CAN between the first and second biopsy (pCAN), while no progression or stable CAN (sCAN) was defined when a decrease or maintained CAN grade was found between the first and second biopsy.

The clinical and biochemical data were recorded at the time of transplantation and at 1 and 6 months post-transplant. Results were expressed as mean values ± SD. An unpaired two-tailed Student *t* test was used to examine differences in mean values between the groups. Chi square analysis was used to compare the categorical variables.

Results

The mean age of the entire cohort of donors and recipients was 59.60 ± 13.11 and 34.40 ± 9.32 years, respectively. Demographic characteristics of patients are summarized in Table 1.

Table 1 – Табела 1

Patients demographic characteristics, matching data, and post-transplant events: frequency of DGF and acute rejection (AR)

Демографски карактеристики на пациентите, податоци за хистокомпатибилност и случувања по трансплантација: стапка на одложената функција на графтот и акутните отфрлања

Donor age (yr)	59.6 ± 13.1
Recipient age (yr)	34.4 ± 9.3
Female/male	15/20
Cause of end-stage renal disease	
Glomerulonephritis	12
Diabetes	0
Hypertensive renal disease	5
Polycystic renal disease	2
Reflux nephropathy	6
Other	10
Time on dialysis (mo)	30.1 ± 37.8
Total HLA mismatch score	2.0 ± 1.2
Mean CIT (h)	3.4 ± 1.3
DGF (%)	10/35 (26%)
AR (%)	7/35 (20%)

Among all the biopsies only 10% (7/70) showed no histopathological lesions. BR was found in 13/35 (37%) and 9/35 (25.7%), and SAR in 11/35 (31.4%) and 17/35 (48.6%) of the patients, at 1 and 6 months biopsies, respectively. The mean histological index (HI), assessed as a total sum of scores for acute and chronic changes, increased from 5.14 ± 3.00 at 1 month to 7.94 ± 3.80 at 6-month biopsy ($p < 0.001$). Similarly, the mean CAN score (sum of histological markers for chronicity) increased significantly from 1 to 6-month biopsy (1.83 ± 1.46 vs. 4.66 ± 2.35; $p < 0.001$). The serum creatinine (sCr) and body weight (BW) increased significantly at 6 months after transplantation, while calculated creatinine clearance (cCrcl) decreased significantly when compared to 1-month values (Table 2).

Of the entire cohort, 24 patients presented with acute histopathological lesions (13 BR + 11 AR type I or II) at 1 month biopsy. Additionally, an increase in serum creatinine between 10 and 20% from baseline value (two weeks prior to the biopsy) was assessed in 3 and 5 patients, respectively. These patients were considered as SAR and therefore pulse corticosteroid therapy was administered (Table 2).

In our study, at the first month biopsies no histological evidence of CAN was found in 62.8%, CAN grade I (according to the Banff classification) was found in 37.2%, while none of the patient had CAN grade II or III. At the 6-month biopsy the proportion of these findings was 14.3%, 37%, 45.8% and CAN grade III in 2.9%, respectively (Table 2).

Table 2 – Табела 2

Biochemical, clinical data and histological findings and scores at 1 and 6 months post-transplantation of all transplant recipients (n=35)

Биохемиски, клинички податоци и хистолошки наоди и скорови на 1 и 6 месеци по трансплантација кај сите реципиенти (н=35)

	1 month		6 month		
parameter	Mean	St Dev	Mean	St Dev	P value
BW recip.	61.9	12.7	64.6	13.9	$p < 0.01$
sCr	122.0	31.7	145.5	45.5	$p < 0.01$
cCrcl	66.6	19.9	58.7	20.8	$p < 0.05$
cg*	0.23	0.43	0.54	0.61	$p < 0.05$
ci*	0.51	0.51	1.40	0.77	$p < 0.01$
ct*	0.49	0.56	1.43	0.74	$p < 0.01$
cv*	0.37	0.49	1.00	0.73	$p < 0.01$

CAN score	1.83	1.46	4.66	2.35	$p < 0.01$
Total HI	5.14	3.00	7.94	3.80	$p < 0.01$

	patients	perc. (%)	patients	perc. (%)	
No lesions	4	16	3	8.6	n.s.
AR	4	11.4	2	5.7	n.s.
BR	13	37	9	25.7	n.s.
SAR	11	31	17	48.6	n.s.

	Percentage (%)	Percentage (%)	
no CAN	62.8	14.3	$p < 0.01$
CAN gr. I	37.2	37	n.s.
CAN gr. II	0	45.8	$p < 0.01$
CAN gr. III	0	2.9	$p < 0.01$

*cg, ci, ct, cv – Banff classification of CAN: chronic glomerulopathy, interstitiopathy, tubulopathy, vasculopathy

On the other hand, CAN was absent in 27/70 (38.6%) at 1 and 6-month biopsies. Further analysis showed progression of CAN in 25/35 (71.4%), while 10/35 (28.6%) of the patients had not progressed from 1 to 6-month biopsy. Thereby, the entire cohort was stratified to progressed CAN (pCAN) group (n = 25; 71.4%) and stable CAN (sCAN) group (n = 10; 28.6%) patients. The groups showed no difference in: donor age and sex, recipient age and sex, number of HLA mismatches, cold ischemia time (CIT), DGF, acute rejection episodes, sCr, cCrcl and proteinuria either at 1 or at 6 months after transplantation (Table 3).

The mean HI score in sCAN group did not increase from 1 to 6-month biopsy (5.5 ± 3.1 *vs* 4.10 ± 3.2). In contrast, HI in pCAN group increased significantly at 6-month biopsy (5.0 ± 3.0 *vs* 9.5 ± 2.8; $p < 0.01$). Additionally, there was an increase in BW (63.11 ± 14.27 *vs* 66.39 ± 15.26; $p < 0.03$) and a decrease in cCrcl (67.45 ± 19.43 *vs* 58.78 ± 19.81; $p < 0.03$) at 6 months in pCAN group (Table 3).

The percentage of BR and SAR between the groups at 1-month biopsy was not different [17/25 (68%) *vs* 7/10 (70%)] in pCAN and sCAN, respectively. However, there was a significant difference in the proportion of treated BR and SAR at 1-month biopsy (23.5 % *vs* 57.1%; $p < 0.05$), as well as in the total score of acute histological lesions (1.08 ± 0.95 *vs* 0.35 ± 0.66; $p < 0.001$) in pCAN and sCAN group at 6-month biopsy, respectively (Table 3).

Table 3 – Табела 3

Biochemical, clinical data and histological findings and scores at 1 and 6 months post-transplantation according to the CAN progression

Биохемиски, клинички податоци и хистолошки наоди и скорови на 1 и 6 месеци по трансплантација согласно со прогресијата на ХАН

	pCAN group (n= 25)		sCAN group (n=10)		
parameter	Mean	St Dev	Mean	St Dev	P value
Donor age	60.2	13.8	58.1	11.7	n.s.
Recipent age	35.6	8.8	31.3	10.4	n.s.
Donor GFR	50.3	16.6	54.1	18.8	n.s.
CIT (h)	3.5	1.5	3.4	0.7	n.s.
HLA mismatch	1.8	1.3	2.4	0.9	n.s.
recip.BW / 1mo	63.1	14.3	58.9	7.3	n.s.
recip.BW / 6mo	66.4	15.3	59.1	6.7	0.07
sCr 1 month	122.6	36.2	120.3	17.3	n.s.
sCr 6 months	147.4	48.8	140.6	38.1	n.s.
cCrcl / 1 mo	67.5	19.4	64.3	21.9	n.s.
cCrcl / 6 mo	58.8	19.8	58.6	24.5	n.s.
proteinuria/1mo	0.77	0.4	0.65	0.4	n.s.
proteinuria/6mo	0.65	0.7	0.45	0.3	n.s.
Ac. lesion core/6mo	1.08	0.95	0.35	0.66	$p < 0.01$
CAN score /1mo	1.6	1.4	2.5	1.6	n.s.
CAN score/6 mo	5.4	1.8	2.7	2.5	$p < 0.01$
HI / 1mo	5.0	3.0	5.5	3.1	n.s.
HI / 6 mo	9.5	2.8	4.1	3.2	$p < 0.01$

	patients	perc. (%)	patients	perc. (%)	
DGF	7	28	3	30	n.s.
AR (early Tx)	5	20	2	20	n.s.
AR /1 mo	4	16	2	20	n.s.
BR+SAR/ 1 mo	17	68	7	70	n.s.
Th/BR+SAR/1mo	4	23.5	4	57.1	$p < 0.01$
AR /6 mo	2 pts	8%	/	/	$p < 0.05$

Following the evolution of histological lesions at 1 and 6-month biopsies, no significant modification in the intensity of acute and chronic lesions was observed in the sCAN group. In contrast, the severity of chronic lesions in

the pCAN group increased in all renal compartments, while the intensity of acute lesions was observed only in the tubulo-interstitial compartment at 6-month biopsies (Table 4).

Table 4 – Табела 4

Evolution of the histological lesions in progressed CAN group

Еволуција на хистолошките лезии кај групата со прогресија на ХАН

	1 month biopsy		6 months biopsy		
Lesion type	Mean	St Dev	Mean	St Dev	P value
g	0.44	0.71	0.32	0.56	n.s.
i	1.28	0.79	1.72	0.68	0.013
t	1.28	0.79	1.76	0.60	0.008
v	0.44	0.71	0.24	0.60	n.s.
ah	0.24	0.44	0.28	0.46	n.s.
cg	0.20	0.41	0.52	0.59	0.043
ci	0.44	0.51	1.72	0.54	0.000
ct	0.40	0.58	1.76	0.52	0.000
cv	0.28	0.46	1.16	0.69	0.000

Discussion

Chronic allograft nephropathy is the most common cause of late allograft failure. Early protocol biopsies revealed that CAN starts early after transplantation [16], clinically presented as a slow decline of renal function. There is increasing evidence that protocol biopsies performed in stable allografts may be a valuable tool for uncovering early clinically unapparent acute histopathological lesions (borderline and subclinical acute rejections), which have been suggested as causes of CAN, leading to deterioration of graft function and ultimately to allograft loss.

The principal finding of this study is the histological evidence of high percentage of clinically silent acute rejections (BR/SAR) in 37 and 31.4%, at 1-month, and in 25.7 and 48.6% at 6-month biopsy, respectively. Comparably, other working groups have also described a high prevalence of BR and SAR. Rush *et al.* noted a 20–50% prevalence of SAR [12, 13], while Schweitzer *et al.* reported prevalence of BR in about 23% and SAR in 33% of the biopsies

performed at 1 month post-transplant [17]. Isoniemi *et al.* [18] demonstrated that chronic lesions were present, even in patients with well-functioning allografts, whether or not they had developed early acute rejection episodes.

Our study showed no histological evidence of CAN in 62.8%, and mild CAN changes (grade I) in the remaining 37.2% of 1-month biopsies. None of the patients was classified as CAN grade II or III. In contrast, at 6-month biopsy the proportion of these findings was 14.3%, 37%, 45.8% and CAN grade III in 2.9%, respectively. These findings correlate with those reported by Seron *et al.* [5].

The progression of CAN at 6-month biopsy was observed in a substantial proportion of 1-month biopsies (71.4%) and the remaining 21.6% of biopsies showed a regreassion of CAN. This finding is in line with the expected probability of histological and clinical deterioration of the graft function. Moreover, about half of the patients who progressed displayed CAN grade II in the second biopsy, followed by CAN grade I. Approximately half of the patients with apparent regression displayed CAN grade I in both, 1 and 6-month biopsies. Hence, these results suggest that biopsies with apparent regression might reflect the difficulty of properly classifyng biopsies with mild interstitial fibrosis and tubular atrophy.

It is well documented in previous studies that subclinical inflammation, scored under the Banff schema as SAR and BR, leads to increased interstitial fibrosis and CAN within the first years [3–7]. Some investigators have expressed concern that the Banff "borderline" finding is indicative of early rejection and that withholding treatment would allow progression of the rejection process [14, 15]. Our data support this view. The present immunological inflammation in a number of untreated borderline changes (n = 8) at 1-month biopsy, and an evolution towards SAR in a substantial proportion of these patients at 6-month biopsy [5/8], might be an additional explanation for progression of CAN in the pCAN group. Moreover, 4 patients in the pCAN group initially diagnosed as SAR (classified as type IIA), showed improvement in histology towards type I AR after pulse corticoid therapy, at 6-month biopsy. This finding is in line with the reports from recent studies that corticosteroid treatment of early subclinical rejection is associated with a better outcome in renal transplant patients [3, 9]. Our study results are in favour of anti-rejection treatment in borderline lesions (BR) that in fact represent a mild form of subclinical acute rejection.

Furthermore, in order to see whether the treatment of BR or SAR detected in 1-month protocol biopsies prevents the development and/or progression of CAN at 6-month biopsy, we have documented that the substantial number of untreated subclinical acute histological lesions in the pCAN group has evolved towards a worsened pathohistological score of acute lesions and CAN grade at 6 months after transplantation. Similarly, and in line with aforementioned observation, is the significant increase in HI and acute histological

lesion score from 1 to 6-month biopsy in the pCAN group of patients. However, despite the progression of renal scarring in the pCAN group, both groups presented with similar serum creatinine at the same time points, but long-term follow-up is awaited. This raises the issue that protocol biopsies of stable allografts may uncover histological signs of SAR/BR and CAN, and may help to establish an individually targeted immunosuppressive regimen, which may include antirejection treatment of subclinical rejection episodes, the use of new less toxic immunosupressants or even reduction or withdrawal of immunosuppressive drugs.

Concerning the risk factors for CAN, the groups did not differ in the clinical data such as mean age, gender and glomerular filtration rate (GFR) of donors and recipients, CIT, number of HLA mismatches, experience of DGF, proteinuria and hyperlipidemia. The incidence of clinical acute rejections (AR) at first month post-transplant was similar in both groups (pCAN; sCAN). The only clinical modification between the groups was an increase of recipient BMI and a decrease in cCrcl in the pCAN group, at 6 months after transplantation.

Our data confirm a frequent histological presence of chronic allograft nephropathy in early protocol biopsies in clinically silent renal transplants. Moreover, the presence of untreated borderline and grade I/IIA acute rejections at the first month protocol biopsies, were associated with an increased proportion of acute rejections and an increased progression of acute and chronic lesions at the 6-month biopsy. Hence, our study showed that corticosteroid treatment of early subclinical acute and borderline rejections is associated with a lower progression of chronic allograft nephropathy. We hypothesize that the beneficial effect of corticosteroids is due to the interruption of early immune and nonimmune process of tissue injury. However, a definitive result from this study concerning the latter histological deterioration and impairment of allograft function could be expected from the 1 and 2 years follow–up results.

While many trials aimed to prevent acute rejection have been done in the last decade, no trials aimed to prevent CAN have been performed. Our finding suggests the need for protocol or surveillance biopsies, to improve the monitoring of immunosuppressive therapy before renal function is irreversibly altered.

Conclusion

In conclusion, 1-month protocol biopsy may be valuable to uncover BR, SAR and the presence of early CAN in stable renal allografts. Progression of CAN at 6-month biopsy was associated with a greater number of untreated BR and SAR at 1-month biopsy. Untreated BR and SAR at 1-month biopsy showed greater susceptibility to acute histological deterioration at the 6-month biopsy, accelerating the progression of chronic allograft nephropathy. This observation

may have important implications for the design of clinical trials aimed to prevent the progression of CAN.

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Р е з и м е

ХРОНИЧНА АЛОГРАФТ НЕФРОПАТИЈА (ХАН) ВО РАНИТЕ ПРОТОКОЛ БУБРЕЖНИ БИОПСИИ: МОЖНА ЛИ Е ПРЕВЕНЦИЈА НА РАЗВОЈОТ И ПРОГРЕСИЈАТА НА ХАН СО ТРЕТМАНОТ НА БОРДЕРЛАЈН И СУБКЛИНИЧКИТЕ АКУТНИ ОТФРЛАЊА

Ј. Масин-Спасовска[1], Г. Спасовски[1], М. Поленаковиќ[1], С. Цикова[1], Г. Петрушевска[2], Б. Димова[2], Љ. Лековски[3], Ж. Попов[3], Н. Ивановски[1]

[1]Клиника за нефрологија, Медицински факултет, Скопје, Р. Македонија
[2]Институт за патологија, Медицински факултет, Скопје, Р. Македонија
[3]Клиника за урологија, Медицински факултет, Скопје, Р. Македонија

Апстракт: Хистолошките маркери за хронична алографт нефропатија (ХАН) во раните протокол биопсии, можат да резултираат со пропаѓање на функцијата на графтот. Целта на студијата беше да се евалуираат факторите на ризик во раните хистолошки наоди за ХАН и да се процени дали третманот на бордерлајн (граничните) и субклиничките акутни отфрлања (БО/САО) на 1 месец по трансплантацијата, го превенира развојот и/или прогресијата на ХАН на 6 месеци.

Направените триесет и пет двојни алографт биопсии во првиот и шестиот месец по трансплантација беа проценети според критериумите на класификацијата Банф 97. Просечниот ХАН скор (збир на хистолошките

маркери за хроницитет) бележеше сигнификантен пораст кај биопсиите направени шестиот месец по трансплантацијата (1.83 ± 1.46 *vs* 4.66 ± 2.35; p < 0.01). 27/70 (38.6%) од биопсиите не покажаа присуство на ХАН, 71.4% покажаа прогресија и 28.6% беа со непроменет ХАН на биопсијата на 6 месеци. При поделбата спрема прогресија, индексот на хроницитет (збир на акутните и хронични хистолошки промени) во групата со прогресија на ХАН (пХАН), беше значајно повисок при биопсијата на 6 месеци (5.0 ± 3.0 *vs* 9.5 ± 2.8; p < 0.01). На биопсијата од првиот месец, БО/САО беа најдени кај 68% и 70%, од пХАН и групата без прогресија т.е. стабилна ХАН (сХАН), соодветно. Процентот на третирани БО/САО во сХАН групата беше значајно повисок (57.1 *vs* 23.5%; p < 0.05), а скорот на акутните хистолошки промени понизок (1.08 ± 0.95 *vs* 0.35 ± 0.66; p < 0.01) на биопсијата на 6 месеци.

Во заклучок, протокол бубрежната биопсија во првиот месец по трансплантација може да ја открие високата преваленца на бордерлајн и субклиничките отфрлања кај пациентите со уредна функција на графтот. Прогресијата на ХАН, покажана во биопсијата на 6 месеци од нашата студија, беше асоцирана со поголем број на нетретирани БО/САО од биопсијата во првиот месец. Ваквата опсервација може да има особена важност за дизајнот на клиничките студии кои имаат за цел да ја превенираат прогресијата на ХАН.

Клучни зборови: трансплантација, алографт биопсија, бордерлајн, субклинички отфрлања, (ХАН) хронична алографт нефропатија, (ХИ) индекс на хроницитет.

Contact address:

Goce B Spasovski, MD, PhD, Sc. Res.
Department of Nephrology
Clinical Center Skopje
University of Skopje
Vodnjanska 17
1000 Skopje
Republic of Macedonia
Mob. phone: +389 70 268 232
Fax: +389 2 3231 501

E-mail: gspas@sonet.com.mk