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Original Article

Spectrum of renal allograft dysfunction in the first post transplantation month from living donors: A histopathological study

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Abstract

Early renal transplant dysfunction is a major problem in the early post-transplantation (post. Tx) phase and is recognized as a major cause of graft loss. This work was designed to identify and differentiate between causes of early renal dysfunction in grafts taken from living donors for accurate diagnosis and better outcome.

Between January 1992, and December 2001, a total of 1398 renal allograft biopsies were referred to us from various renal units mostly in Greater Cairo area. Three hundred biopsies, obtained from 287 patients and performed within the first post Tx. month were included in this study. The clinical data were collected from patients' files and new 3 μ sections (30 serial) were prepared from the paraffin blocks.

All the studied cases were from living donors and 9.4% of them were living related. The cause of ESRD was unknown in 72.4% of cases and out of the known causes chronic interstitial nephritis and hypertension were the most common. The main indications for the allograft biopsies were impaired graft function (IGF 71.5%), while delayed graft function (DGF) was the cause in 3.1% of the cases.

The main diagnostic categories were acute rejection (AR 38%), acute tubular necrosis (ATN 23.7%) and tubular injury (23.3%). Infarction and cortical necrosis constituted 15.7% of the cases and 21.3% of them were associated with AR. Evidence of drug toxicity were detected in 9% of cases, while thrombotic microangiopathy was detected in 5 cases (1.6%) and related to cyclosporine (CSA) in 4 of them. Chronic allograft changes were detected in 6.3% of the cases and focal segmental glomerulosclerosis FSGS in one case.

Cellular rejection was the most common type of AR (68%), mixed cellular and vascular R were detected in 2.3% of cases, and low grades of R were the commonest grades (IA 69.3% and IIA 69.6%).

It was found that ATN was the most common category in the first week (28.8%) and accounting for 70% of DGF cases, while the frequency of tubular affection (ATN + tubular injury) statistically decreases by time, that of AR significantly increases by time. On comparing ATN and AR, significant differences were detected between them as regards to the clinical presentation, serum creatinine (0.007) and in their frequency in the 2nd and last 2 weeks (P=0.02 and 0.0001). It is worth noting that 42.3% of ATN cases were associated with other pathological lesions (66.7% of them were associated with AR) which may modulate the line of treatment.

In conclusion, ATN and AR were the most common categories of early renal allograft dysfunction, however other pathological lesions, per se or coincide with the main categories may be the cause. So adequate allograft biopsy and full clinical data are helpful in differentiation between the causes and in establishment of a proper treatment protocol. Also, zero hour biopsies are recommended to provide base line information.

Key words: Dysfunction; graft; kidney; rejection

Introduction

Renal allograft biopsy has long been established as the gold standard to distinguish between rejection and other causes of renal dysfunction in the early post Tx. period. Biopsies that show an absence of rejection are useful in that they prevent unnecessary immunosuppressive pulse therapy and have led to reduced complication rates from over-immunosuppression [1].

Acute failure of the transplanted kidney is a major problem in the early post.Tx. phase and is recognized as a major cause of graft loss. Early renal tx. dysfunction is mainly due to ischaemic damage (acute tubular necrosis), rejection, infection and drug toxicity [2].

Renal allograft biopsies have been more important since introduction of cyclosporine (CSA) and tacrolimus (TAC), because their nephrotoxic properties make the clinical diagnosis of rejection more difficult [3]. In

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addition, histologically they produce tubular injury, which may be mistaken with acute tubular necrosis (ATN), or induce arteriolar changes which may be improperly diagnosed as vascular rejection [4].
For these reasons, it is of considerable interest to identify and differentiate between causes of acute graft failure or early impaired graft function. This work was designed to assess the causes of early graft dysfunction in living renal allograft biopsies in the first post tx month for accurate diagnosis and better outcome.

Material and methods

A retrospective analysis was done on consecutive renal allograft biopsies referred to us (MRF) from various renal units mostly in Greater Cairo area, from January 1992 to December 2001 in search of biopsies performed in first post. Tx month.
The cases were collected as paraffin blocks and new 3μ sections were prepared (30 serial sections from each block) and stained with haematoxylin and eosin (Hx & E), periodic acid schiff (PAS) and masson trichrome stains. They are analyzed by two pathologists using light microscopy to evaluate:

1. Adequacy of the biopsy according to Banff 1997 [5]. They were classified into cases with adequate requirement (10 glomeruli - 2 arteries) and with minimal requirement (7 glomeruli - one artery). The rest was considered as not suitable for Banff.
2. The biopsies were categorized into the following groups based on the histopathology:
   a. Acute tubular necrosis (ATN) and tubular injury according to Olsen (1989)[6].
   b. Acute rejection and borderline changes: Each biopsy was scored using the Banff 1997 [5] criteria for semi-quantitative grading (0-3+) of glomerulitis (g), interstitial inflammation (i), tubulitis (t), vasculitis (v), and classified by type and severity of rejection.

Table 1. Banff 1997 diagnostic categories for renal allograft biopsies

Type (grade)	*Histopathological Findings*
Borderline changes	Cases with mild tubulitis (t1) and mild interstitial infiltrate (i1), no intimal arteritis (v0)
Acute / active rejection	
IA	Cases with i2, t2
IB	Cases with i2, t3
IIA	Cases with v1
IIB	Cases with v2
III	Cases with v3

   c. Hyperacute rejection.
   d. Infarction and cortical necrosis.
   e. Drug toxicity: cyclosporine (CSA) and TAC manifested by small isometric vacuolation associated with epithelial injury (in proximal convoluted tubules) and arteriolar myocyte vacuolations. Acute arteriolopathy characterized by endothelial shedding, eosinophilic globules in the media or scattered thrombi [7].
   f. Thrombotic microangiopathy: characterized by thrombosis in the afferent arterioles and adjacent glomerular capillary loops [8].
   g. Others.

Clinical data

The medical records of the patients were reviewed and the following data were included:

1. Age and sex.
2. The cause of end stage renal disease (ESRD) if reported.
3. Graft type (living related versus living unrelated).
4. Serum creatinine level (SCr).
5. The clinical indications for the graft biopsy.
6. The diagnosis suspected by Doppler if present.
7. Post Tx. time of the biopsy, and the number of biopsies if more than one was done in the first month.

The data were analyzed using a standard chi-square test.

Results

From a total of 1398 renal allograft biopsies obtained from 1992-2001, 327 biopsies were performed in the first post. Tx month and were included in this study. They were obtained from 287 patients, thus 35 patients had repeated biopsies and five of them had three biopsies.
The age range at the time of biopsy was 16-65 years and male to female ratio 1.8: 1.
In 72.4% of cases, the etiology of ESRD was unknown, however chronic interstitial nephritis and hypertension were the most common known causes (table 2). In 10 cases, the graft was the 2nd one. All the studied cases were from living donors, since there is no cadaveric Tx. in Egypt. As regard, the type of the graft, it was living related in 9.4% and the rest were living non-related.

Table 2. The etiology of end stage renal disease in the studied cases

Original disease	*No.*	*%*
Hypertensive nephrosclerosis	18	6.3%
Diabetes mellitus	12	4.2%
Lupus nephritis	10	3.5%
Chronic glomerulonephritis	8	2.8%
Chronic interstitial nephritis	20	7%
Hyperoxalosis	3	1%
Amyloidosis	2	0.7%
Haemolytic uraemic syndrome	4	1.4%
Hereditary nephritis	2	0.7%
Unknown	208	72.4%
Total	287	100%

The level of serum creatinine was reported in 132 cases only and its range was 1.2-11.7 mg/dl.
Table 3 showed, the clinical indications for the biopsies (327 biopsies), where 71.6% were for impaired graft

function (IGF). In 8.6%, the biopsies were taken for follow-up due to poor response to treatment. In 10 cases, there were failure of the graft to function (delayed GF) and in 5 of them the cause was related to the operative procedure as intraoperative arterial spasm (3 cases) and perinephric haematoma (in 2 cases).

Eight cases were diagnosed by Doppler prior to biopsy. Four of which were diagnosed as normal and were proved histologically to be tubular injury or ATN. The other four were suspected to be vascular insufficiency and were proved to be infarction or vascular rejection.

Table 3. Clinical indications for renal allograft biopsy in the studied biopsies

Clinical indications	*No.*	*%*
IGF	234	71.6%
Delayed GF (DGF)	10	3.1%
Haematuria	5	1.5%
Anuria / severe oliguria	23	7%
Follow-up biopsy	28	8.6%
Failed previous biopsy	27	8.2%
Total	327	100%

As regards to the adequacy of the allograft biopsy according to Banff 1997 [5], 24.8% were of adequate requirement, 33.8% of minimal requirement and 41.4% not suitable for Banff-Scoring.

Table 4 showed, the diagnostic categories of the studied biopsies where acute rejection was the most common cause accounting for 38%. However, if ATN (Fig. 1) and tubular injury were considered as one group. They constituted the most common cause accounting for about 50% of the causes.

As regards to the types and grade of AR, cellular rejection was the most common type accounting for 62% of them. When the grades were considered low grades of both cellular and vascular rejection was the most common type as grade IA constituted 69.3% of cellular rejection (Fig. 2) and IIA constituted 69.8% of vascular rejection. Severe rejection (grade III) was detected in 10.9% of vascular rejection (Fig. 3).

Table 4. Diagnostic categories of renal allograft biopsies

Diagnostic category	*No.*	*%*
ATN	71	23.7%
Tubular injury	70	23.3%
Drug toxicity	17	5.7%
Borderline changes	46	15.3%
Acute rejection (AR)	114	38%
Cellular (68)		
Vascular (39)		
Combined (7)		
Infarction / cortical necrosis	47	15.7%
Thrombotic microangiopathy	6	2%
Hyperacute rejection	2	0.7%
Others	42	14%
Total	300	100%

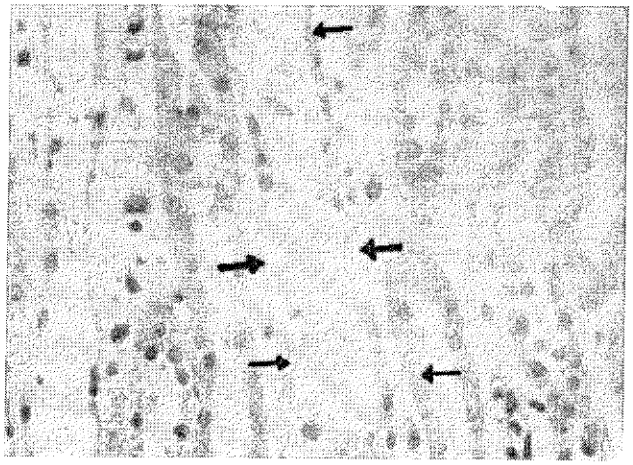

Fig. 1. A case of ATN shows dilatation of the tubules, many necrotic anucleated cells (thin arrows) and areas of shedding epithelium (thick arrows) (Hx & E X400)

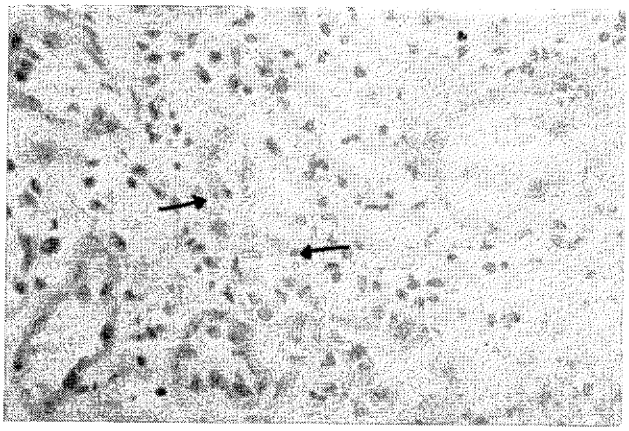

Fig. 2. A case of cellular rejection (grade IA) showing moderate tubulitis (t2-arrows) [Hx & E X200]

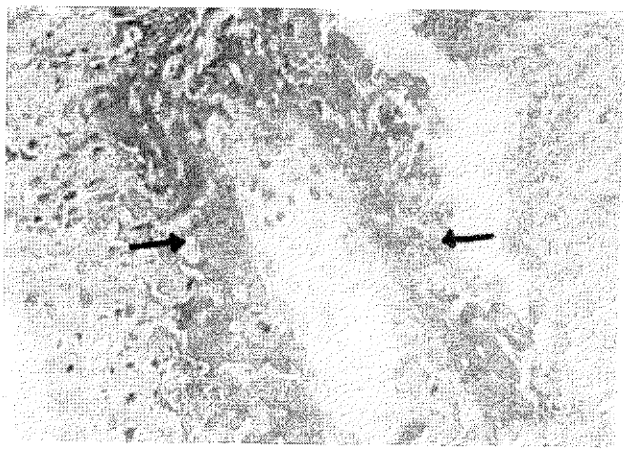

Fig. 3. A case of severe vascular rejection (grade III) showing fibrinoid necrosis (arrows) and inflammatory infiltrates (PAS X 400)

Other diagnoses include oxalosis (6 cases), no change (3 cases), acute suppurative interstitial nephritis (2 cases), fungal infection (1 case), viral infection (2 cases) and FSGS (1 case). Chronic changes were detected in 19 cases (6.3%), in the form of transplant glomerulopathy (3 cases), mild interstitial collagenosis (6 cases), tubular atrophy (7 cases) and early chronic vascular changes (3 cases).

It was found that 30 cases of ATN (42.3%) were associated with other pathological lesions. The most common one was AR (66.7%).

When comparison was done between the frequency of the diagnostic categories at different intervals in the 1st month (table 5),it was found that ATN was the most common category in the 1st week (28.8%), while AR was the most common one in the 2nd and last 2 weeks (35.8%, 66.3% respectively). In addition 45% of cases of ATN (32/71) occurred in the 1st week. If ATN and tubular injury were considered as one group (tubular affection 141 cases), the difference between its frequency and that of AR in the 1st and last 2 weeks was highly significant (P=0.0001, 0.01 respectively).

It was found that the frequency of tubular affection statistically decreased with time, while that of AR statistically increase by time (the difference between 1st, 2nd w, last 2 weeks in tubular affection and rejection were 0.0002 & 0.0007 and 0.005 & 0.0001 respectively).

Table 5. Comparison between the frequency of the diagnostic categories at different intervals (week)

Diagnostic Categories (n)	*Different Interval*					
	1st week		2nd week		Last 2 weeks	
	No.	%	No.	%	No.	%
ATN (71)	32	28.8%	23	21.7%	16	19.2%
Tubular injury (70)	25	22.5%	22	20.8%	23	27.7%
Drug toxicity (17)	6	5.4%	6	5.7%	5	6.0%
Borderline changes (46)	13	11.7%	18	16.9%	15	18%
Acute rejection (114)	21	18.9%	38	35.8%	55	66.3%
Infarction / cortical necrosis (47)	13	11.7%	14	13.2%	20	24.1%
Thrombotic micro-angiopathy (6)	2	1.8%	2	1.9%	2	2.4%
Hyperacute R. (2)	2		-		-	
Total	111	100%	106	100%	83	100%

When comparison was done between ATN and AR (table 6), significant differences between both were detected in SCr levels and in their frequencies in the 2nd and last 2 weeks. Although both categories were encountered in cases presenting with IGF, however AR was statistically higher (P<0.0001) constituting 47% of them. In contrast 70% of cases with DGF were ATN and no cases of AR responsible for DGF. In addition, ATN was statistically higher in cases presenting with anuria / severe oliguria than AR.

Infarction and cortical necrosis were detected in 47 cases representing 15.7%. Ten of them (21.3%) were associated with rejection, four cases associated with vascular occlusion and one with thrombotic microangiopathy (Fig. 4). In the others, the cause of infarction was not known.

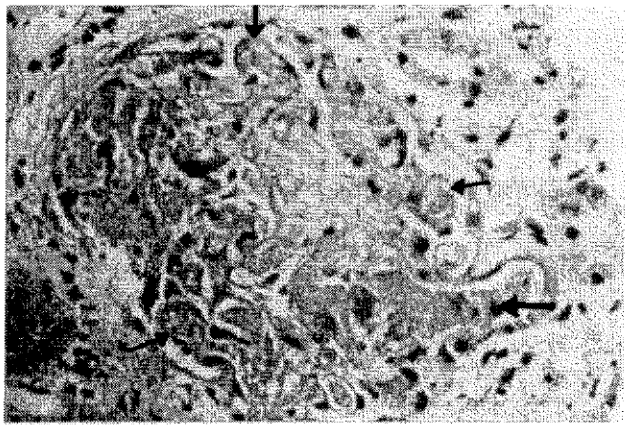

Fig. 4. A case of thrombotic microangiopathy showing thrombi in afferent arterioles (thick arrow) and glomerular capillaries (thin arrows) [Hx & E X400]

Table 6. Comparison between ATN and AR

	ATN	*AR*	*P*
Biopsy (n)	71 (23.7%)	114 (38 %)	
Age at biopsy range	17-60	16-60	
Post tx. Interval (w):			
Range	Immediate-1 month	3rd day-1 month	
1st w (111)	32	21	0.06
2nd w (106)	23	38	0.02
Last 2 weeks (83)	16	55	0.0001
Serum creatinine:			
Range (mg/dl)	1.7-9.9	1.7-9.3	
Mean	5.54	3.56	0.007
S.D.	±2.28	±1.9	
Indication for biopsy:			0.0001
IGF (234)	46 (19.7%)	110 (47%)	
DGF (10)	7 (70%)	-	0.001
Anuria /severe oliguria (23)	15 (65.2%)	2 (13.3%)	0.0001
Hematuria (5)	3 (60%)	2 (40%)	0.5

Discussion

Kidney transplantation is the method of choice for treatment of ESRD, however the long term graft survival represents only about 50% due to various types of lesions occuring in the graft. The early diagnosis of AR provides useful information in differentiation from other causes of graft dysfunction. In addition, the early diagnosis with subsequent adequate management decreases the risk for future chronic rejection nephropathy [9].

This study was designed to analyze histologically the renal allograft biopsies in 1st post. Tx. month in living donors in an attempt to determine and differentiate between causes of early graft dysfunction for accurate diagnosis and better outcome.

Between January 1992 and December 2001, 327 renal allograft biopsies were obtained from 286 patients in 1st post tx. month. In about 73% of cases, the etiology of ESRD was unknown. This was in accordance with Ismail 2001 [10]. Among the known causes chronic interstitial nephritis followed by hypertensive nephrosclerosis were the most common. This finding was in accordance with that of Barsoum and Francis 2000 [11] and may indicate the significant role of environmental pollution in development of chronic renal failure in Egypt. Munter et al., 2003 [12] found that exposure to lead, even in low levels is associated with development of ESRD.

Most studies agree with the usefulness of renal transplant biopsy in the early post. Tx. period which is usually performed because of episodes of IGF or delayed GF [1&13]. These were in accordance with the present findings as IGF was the most common indication for the biopsy (71.6%) followed by repeated allograft biopsy for poor response to treatment. The latter may be related to the adequacy of the previous biopsy as 41.4% of the biopsies were not suitable for Banff scoring.

As regards to the frequency of the diagnostic categories, AR was the most common cause accounting for 38%. This finding was lower than that reported by Kon et al. 1997 [1], (43%). This discrepancy may be attributed to many factors. First; in their study, they included biopsies done in the 1st three months, while this study included those done in 1st month only and we found that the frequency of AR significantly increases with post. Tx. period. Second; they studied 117 biopsies and the present work was on 300 biopsies. Lastly, they didn't mention if they included borderline category with cases of rejection or not.

The frequency of ATN in the present work was 23.7%, however if tubular injury is included with ATN, the frequency will be 47%. Sens et al. 1999 [14], reported an ATN frequency of 65%. The discrepancy may be related to their small sample (20 biopsy) and shorter post tx. period (1st 20 days). As the significant decrease in frequency of ATN was detected in the present work.

Ischaemic injury to the donor organ during harvesting and subsequent transplantation into the patient, is a common cause of oliguria /anuria in the immediate post-Tx. period. In the present study, ATN was responsible for 70% of delayed GF and 65.2% of oliguria / anuria and 45% of ATN was detected in the 1st week. In addition, the frequency of tubular affection (ATN and tubular injury) was significantly higher than that of the rejection in the 1st week. This was in accordance with Olsen et al. 1989 and Sens et al. 1999 [6,14].

Although the diagnosis of ATN is important because it is self-limited and recovery ensues usually within few weeks, careful histological examination of the biopsy should be done because ATN may be associated with other pathological lesions. In the present work, 42.3% of ATN cases were associated with other lesions. It is worth noting that 66.7% of them were associated with AR and borderline change, which were of critical value as they modulate the treatment.

Tubular injury is a heterogeneous group; it may be related to ischaemia, immunologic reaction, drug toxicity or viral infection. It may be detected during the course of ATN or resolving rejection. CSA and TAC toxicity produce tubular injury with characteristic isometric vacuolation [8]. Viral infection includes cytomegalovirus or polyoma virus. The intranuclear inclusions in the latter are basophilic and homogenous [15,16].

CSA is an immunosuppressive agent that has revolutionized organ transplantation. However, a major limitation to its clinical use is nephrotoxicity. The mechanism of nephrotoxicity was previously thought to be hemodynamic in origin, but there is accumulating evidence for a direct tubular effect. It alternates the tubular morphology, induces apoptosis at low doses and necrosis at high dosage [17]. Recently, Kiely et al. 2003, [18] found in an experimental study that CSA affects the barrier function of renal epithelial cells. CSA and TAC share closely related mechanisms of action, which is parallel by an overlap in the toxicity profile of these two drugs [19].

In the present study, drug toxicity was diagnosed in 9% of cases. This was in accordance with Sens et al. 1999 [14], but it was much lower than that reported by Kon et al. 1997 [1]. The difference with the latter may be attributed to post tx. period as they included cases done in the 1st 3 months. In addition, they didn't mention the criteria used for the diagnosis of CSA toxicity. In the present work, tubular and arteriolar affection must be detected before considering the case as drug toxicity.

Hourmant et al. 1995 [4], reported cases of histologically and clinically unusual acute renal dysfunction in kidney recipient (1.23%). Clinically, it was characterized by early timing, sudden occurrence in patients with good graft function and lead to renal failure in a few days. Histologically, it was similar to haemolytic uraemic syndrome (HUS) with no evidence of graft vessels thrombosis. So, it was termed thrombotic microangiopathy. The etiology was unknown, however bacterial, viral or CSA toxicity were suspected. These findings were in accordance with the present results as it constituted 1.6% of our cases. As regards, the etiology one case had history of original HUS prior to transplantation. The remaining four cases had received CSA, one of them showed histological evidence of CSA toxicity and another had clinical evidence of CSA over dosage. The last two cases had no evidence of CSA

toxicity (clinical or histological) but their SCr levels were improved on reduction of CSA. These findings were in accordance with Nadasdy 1997 [8], who reported that in absence of vascular rejection, glomerular thrombosis should be considered as thrombotic microangiopathy. After exclusion of recurrent HUS, the possibility of CSA toxicity should be raised with substantial reduction or discontinuation of CSA.

In the present work, oxalate deposition was detected in 6 cases (2%), two cases of which had primary hyperoxalosis prior to transplantation. This was in accordance with Bilgin et al. 1999 [20].

In the present work, early chronic graft changes were detected in 6.33% of cases and FSGS was detected in one case. These findings were in accordance with Burke 1995 [3] who reported chronic vascular changes and interstitial fibrosis as early as 1st post. Tx. month and also in accordance with Andresdottir et al. 2000(21), who reported recurrent glomerulonephritis (GN) after 7 weeks. Mathew 1988 [22], explained the early development of FSGS (even within 1st few days) by the presence of a circulating factor.

The presence of these chronic changes in early post. Tx. period raises the value of "zero hour" biopsy (biopsy of donor kidney immediately after vascular anastomosis). It is useful in assessing the state of the donor kidney and provides a histological baseline, when the need arises for performing a subsequent graft biopsy. Szakaly et al. 2001 [23], studied 115 zero hour biopsies and they found that only 38.3% showed no morphological abnormalities. They found ATN (with subsequent delayed GF) in 24.4%, atherosclerosis in 22.6% and GN in 9.6%. Also, Dragun et al. 2000 [24], found that the early inflammation in the graft after ischaemia reperfusion injury is largely independent of the immunologic background and thus immunosuppression with CSA didn't reverse them.

Infarction and cortical necrosis were detected in 15.7% of cases. Ten of them (21.3%) were associated with rejection and 8.5% were associated with vascular occlusion. Thus in 68% of cases of infarction, the cause could not be detected. Nadasdy 1997 [8], reported that infarction was most frequently the consequence of acute vascular rejection. The discrepancy may be related to the fact that the infarction even if small may occupy the major portion of graft biopsy and sometimes the biopsy may not be representative of what is occurring throughout the kidney.

In conclusion, although ATN and AR are the most common causes of early renal graft dysfunction, other pathological lesions, per se or coincide with them, may be the cause. So adequate allograft biopsy and full clinical data are helpful in differentiation between the causes and in establishment of proper treatment protocols. Zero hour biopsies are recommended to provide baseline information.

References

1. Kon, S.P., Templar, J., Dodd, S.; Rudge, J. and Raftery, M.: Diagnostic contribution of renal allograft biopsies at various intervals after transplantation. Transplant, 1997; 63(4):547.
2. Wiecek, A., Nowicki, M., Kokot, F. and Ritz, F.: Acute failure of the transplanted kidney. Pathophysiology, diagnosis and prevention. Ann. Transplant., 1996; 1(4):5.
3. Burke, J., Pirsch, J., Ramos, E., et al.: Long term efficacy and safety of cyclosporine in renal transplant recipients. N. Engl. J. Med., 1994; 331:358.
4. Hourmant, M.; Buzelin, F., Dantal, J., et al.: Late acute failure of well-HLA-matched renal allografts with capillary congestion and arteriolar thrombi. Transplant., 1995; 60(11):1252.
5. Racusen LC, Solez K, Colvin RB, et al.: The Banff 97 working classification of renal allograft pathology. Kid. Int., 1999; 55:713.
6. Olsen S, Burdick J and Keown P: Primary acute renal failure (acute tubular necrosis) in the transplanted kidney. Morphology and Pathogenesis. Medicine, 1989; 68:173.
7. Randhawa P.S., Starzl, T.E. and Demetris, A.J.: Tacrolimus associated renal pathology. Adv. Anat. Pathol., 1997; 4:265.
8. Nadasdy, T.: Transplantation in Renal Biopsy interpretation, edited by Silva F., D'Agati V., and Nadasdy T., New York, Churchill-Livingstone, 1997; pp. 373-401.
9. Krejci K.: Selected prognostic factors of long term renal graft function. Acta. Univ. Palacki. Olomuc. Fac., Med., 1999; 142:19.
10. Ismail, W.M.: Characterization of the cellular infiltration in cases of acute and borderline renal allograft rejection and its impact on graft dysfunction. Thesis submitted for partial fulfillment of M.Sc. Degree in Pathology, 2001; p. 91.
11. Barsoum, R.S. and Francis, M.R.: Spectrum of glomerulonephritis in Egypt. Saudi J. Kid. Dis. and Transplant, 2000; 11(3):421.
12. Muntner, P.; He, J.; Vupputuri, S.; et al.: Blood lead and chronic kidney disease in the general United States population. Kid. Int., 2003; 633:1044.
13. Matas, A.J.; Tellis, V.A.; Sablay, L.; et al.: The value of needle renal allograft biopsy: A retrospective study. Surgery, 1985; 98:922.
14. Sens, Y.A.; deAndrade, R.L., Bastos, R.M., Filho, D.M.; et al.: Duplex Doppler ultrasonography in the dysfunction of early renal allografts: Correlation with renal histopathology. Transplant. Proc., 1999; 31:3009.
15. Pappo, O.; Demetris, A.J.; Raikow, R.B.; et al.: Human polyoma virus infection of renal allografts: Histopathological diagnosis, clinical significance and literature review. Mod. Pathol., 1996; 9(2):105.
16. Randhawa, P.S.; Finkelstein, S.; Scantlebury, V.; et al.: Human polyoma virus interstitial nephritis in the allograft kidney. Transplant., 1999; 67:103.
17. Healy, E.; Dempsey, M., Lally, C. and Ryan, M.P.: Apoptosis and necrosis: Mechanisms of cell death induced by cyclosporine A in a renal proximal tubular cell line. Kid. Int., 1998; 54:1955.
18. Kiely, B., Feldman, G. and Ryan, M.: Modulation of renal epithelial barrier function by mitogen-activated, protein kinases: Mechanism of cyclosporine A-induced increase in transepithelial resistance. Kid. Int., 2003; 63:908.
19. Randhawa, P.S.; Shapiro, R.; Jordan, M.L.; et al.: The histopathological changes associated with allograft rejection and drug toxicity in renal transplant recipients maintained on Tacrolimus. Am. J. Surg. Pathol., 1993; 17:60.
20. Bilgin, N.; Tirnaksiz, M.B.; Moray, G.; Karakayali, H.; et al.: Early recurrence of oxalate deposition after renal transplantation in a patient with primary hyperoxaluria. Transplant. Proc., 1999; 31(8):3219.
21. Andresdottir, M.B.; Assmann, K.J.; Hilbrands, L.B. and Welzels, J.F.: Type I membranoproliferative glomerulonephritis in a renal allograft: A recurrence induced by a cytomegalovirus infection. Am. J. Kid. Dis., 2000; 35(2):6.
22. Mathew, T.H.: Recurrence of disease following renal transplantation. Am. J. Kid. Dis., 1988; 12(2):85.
23. Szakaly, P.; Magyarlaki, T. and Kalmar, N.K.: Clinical value of "zero-hour" biopsy in kidney transplantation. Transplant. 2001, 71(11): 1510.
24. Dragun, D., Hoff, U.; Park, J.K.; Qun, Y.; et al.: Ischaemia-reperfusion injury in renal transplantation is independent of the immunologic background. Kid. Int., 2000; 58(5):2156.