

A Novel, Semiquantitative, Clinically Correlated Calcineurin Inhibitor Toxicity Score for Renal Allograft Biopsies

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Calcineurin inhibitor toxicity (CNIT) is an important cause of chronic allograft nephropathy (CAN), but clinically relevant, diagnostic pathologic criteria remain to be defined. A semiquantitative, clinically correlative CNIT scoring system was developed and validated by pathologic analyses of 254 renal transplant biopsies that were obtained from 50 consecutive pediatric renal transplant recipients. Differentially weighted pathologic criteria (glomerulosclerosis, tubular atrophy, arteriolar medial hyaline, and tubular isometric vacuolization) contributed to the composite CNIT model score. Unlike other established pathology chronicity scores, such as the chronic allograft damage index, Banff, and modified Banff, the CNIT score was highly correlated with future graft function. The 3-mo CNIT score correlated significantly with 12 mo ($P = 0.021$) and 24 mo ($P = 0.03$) calculated creatinine clearance. Arteriolar medial hyalinosis seems to be the most important factor contributing to the clinical impact of the CNIT score.

Clin J Am Soc Nephrol 2: 135–142, 2007. doi: 10.2215/CJN.01320406

Long-term graft loss remains a problem in the field of solid-organ transplantation, especially kidney transplantation (1). The two most frequent causes of chronic allograft nephropathy (CAN) are chronic rejection (CR) and calcineurin inhibitor toxicity (CNIT). A definite diagnosis of CR often is difficult to render on an allograft biopsy, and nonspecific findings of interstitial fibrosis and tubular atrophy can translate to a diagnosis of CAN of unclear etiology.

Recent data have provided evidence that CNIT is a very important cause of CAN, especially after the first posttransplantation year (2,3). In this report, a novel semiquantitative pathologic scoring system for CNIT was developed and correlated with graft function and recipient hypertension (4,5). The score was validated further for its clinical applicability on an independent group of CNIT biopsies.

Materials and Methods

The study population consisted of 50 consecutive pediatric renal transplant recipients (1 to 21 yr of age) who were enrolled in a steroid-free immunosuppression protocol at Stanford University Medical Center (6,7) from 1999 to 2004. Protocol kidney biopsies were performed as standard of care at 0, 3, 6, 12, and 24 mo after transplantation, as well as at the time of clinical graft dysfunction for suspected acute rejection.

All biopsies were reviewed retrospectively by a renal pathologist (N.K.) and two pathology research associates (S.N. and S.S.) who were blinded to clinical information. Five main clinical categories were de-

defined: (1) Acute rejection (8,9), (2) CR with transplant glomerulopathy or arteriopathy (8,9), (3) CNIT (10), (4) CAN (any tubular atrophy or interstitial fibrosis >5% of cortex and of unclear cause) (8,11), and (5) no significant abnormality (no tubular atrophy or interstitial fibrosis <5% of cortex). Other categories included recurrent glomerulonephritis, reflux nephropathy, and acute tubular necrosis.

Given the integral component of chronic injury with CNIT, the chronicity scoring criteria for the CNIT score were chosen similar to the Banff 1997 chronicity scores (8), with additional criteria reflective of acute CNIT injury. The CNIT score was rendered on biopsies with diagnostic features of CNIT: Isometric tubular vacuolization (tv), peripheral or medial arteriolar hyaline (ah), and striped interstitial fibrosis (Figure 1). Other features, such as ischemic collapse of glomeruli, juxtaglomerular apparatus hyperplasia, and tubular dystrophic calcifications, were sought, and, when identified, a careful search for the diagnostic features of CNIT was performed. The CNIT score is based on six parameters that are graded semiquantitatively (scale 0 to 3), resulting in a possible total score of 18 (Table 1). For grading the severity of the chronic changes, all biopsies were scored in a semiquantitative manner to provide a Banff Chronicity Score (BChS), a modified Banff Chronicity Score (MBChS), and a chronic allograft damage index (CADI) (12–15). The components of BChS included transplant glomerulopathy (cg), tubular atrophy (ct), interstitial fibrosis (ci), and chronic vascular changes (cv) (8). The MBChS was calculated using the components of glomerulosclerosis (gs), ct, ci, and cv. The CADI was calculated on a different scale (Figure 2 legend) (12–15).

Immunohistochemical stains were performed on all biopsies with available additional material, using an antibody directed against human C4d. Formalin-fixed, paraffin-embedded tissue was stained with polyclonal antiserum to C4d (16).

The following clinical data were obtained at all biopsy time points: Creatinine clearance (CrCl), calculated by Schwartz method in ml/min per 1.73 m² (17); number of antihypertensive medications required to maintain normal BP; proteinuria, as measured by random urine protein:creatinine ratios (normal <0.2); and the CNI (tacrolimus) trough level (ng/ml) and dosage (mg/kg).

Received April 24, 2006. Accepted September 15, 2006.

Published online ahead of print. Publication date available at www.cjasn.org.

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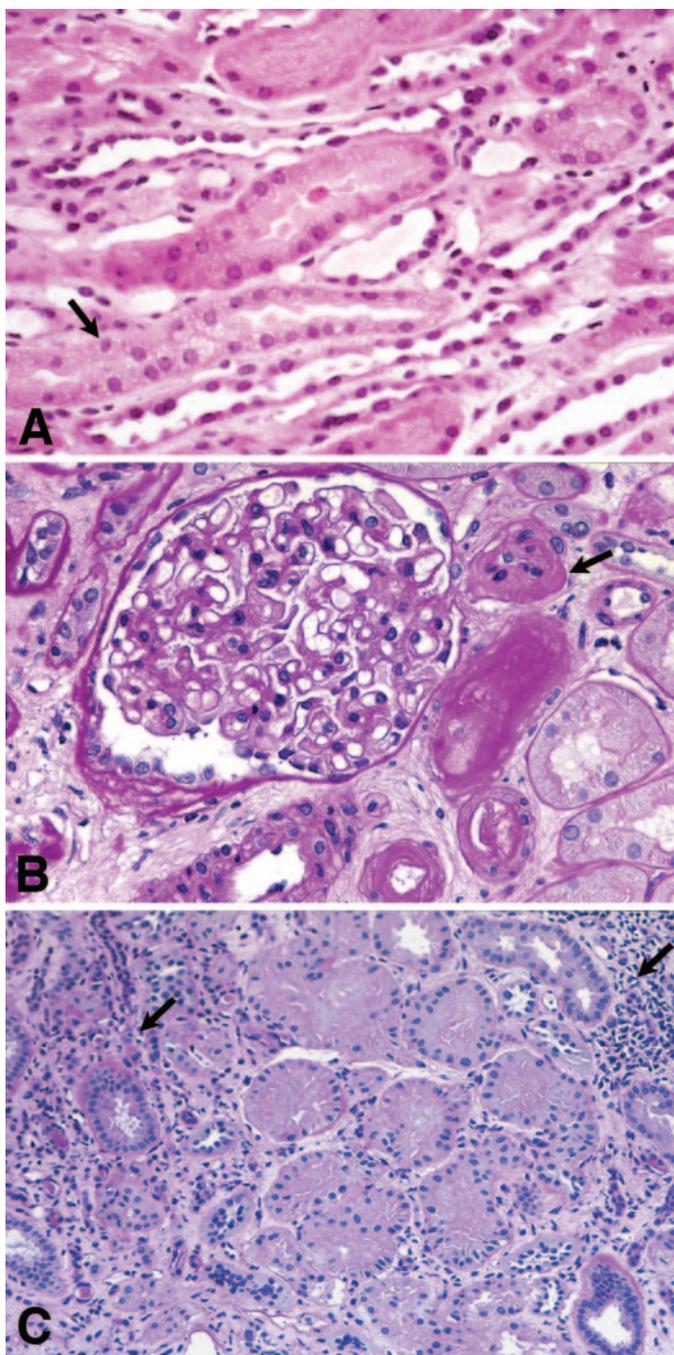


Figure 1. Some of the characteristic features used for diagnosing and scoring calcineurin inhibitor toxicity (CNIT). (A) Proximal tubules with cytoplasmic isometric vacuoles. (B) Afferent arteriolar hyaline (ah) in subendothelial, medial, and peripheral locations. The efferent arteriole seems unaffected, and the glomerulus shows slight retraction of the capillary tuft, likely as a result of ischemia. (C) Tubular atrophy with a striped pattern of interstitial fibrosis.

Statistical Analyses

Multivariate analyses, such as multiple linear regression and multiple logistic regression, were used to model the probability of the CNIT score on the basis of each independent factor and to determine the percentage of variance in outcome variables explained by the indepen-

Table 1. Calculation of CNIT score based on six histologic features of CNIT^a

Histologic Feature	Extent	Score (0 to 3)
Tubular isometric vacuoles	None	0
	1 to 25%	1
	26 to 50%	2
	>50%	3
Interstitial fibrosis	0 to 5%	0
	6 to 25%	1
	26 to 50%	2
	>50%	3
Arteriolar medial hyalinosis	None	0
	10% or fewer arterioles	1
	11 to 30% of arterioles	2
Glomerulosclerosis	>30% arterioles	3
	None	0
	1 to 25%	1
Tubular atrophy	26 to 50%	2
	>50%	3
	None	0
Mesangial matrix increase	1 to 25%	1
	26 to 50%	2
	>50%	3
Total score		18

^aCNIT, calcineurin inhibitor toxicity.

dent factor. The *t*, χ^2 , and Fisher exact tests were used for numeric and categorical variables. *P* < 0.05 was considered significant. Statistical analysis was performed using SAS 9.1 (SAS Institute, Cary, NC). Data are means \pm SD.

Results

Forty-five patients were recipients of living-donor grafts, and five were recipients of deceased-donor grafts. All grafts had immediate function. The mean patient follow-up period was 25.7 mo (range 24 to 44 mo). Of the 50 study patients, two died from unrelated causes with normal functioning grafts (at 8 and 14 mo after transplantation). A total of 254 allograft biopsies were reviewed.

Engraftment, or Day 0, Biopsies

Twenty-three samples were day 0 engraftment biopsies (donor age 18 to 50 yr; mean 34.3 yr). Approximately half of them had fewer than seven glomeruli and therefore were inadequate by Banff criteria. Four of 23 biopsies had mild glomerulosclerosis, ranging from 5 to 20% of glomeruli sampled and with 5% tubular atrophy. The engraftment biopsies were reviewed but not included during the process of building the CNIT score.

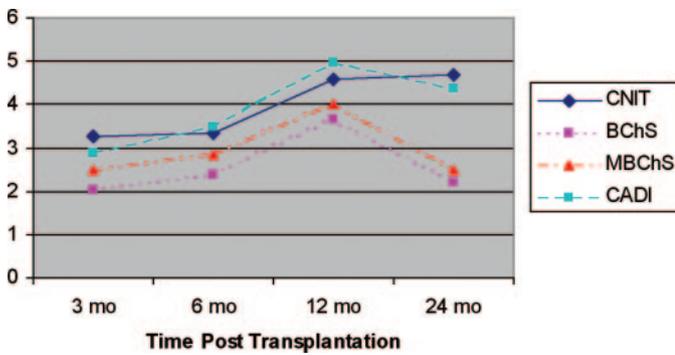


Figure 2. Mean CNIT and other chronicity scores at different study points after transplantation. CNIT, CNIT score; BChS, Banff chronicity score (transplant glomerulopathy [cg] + interstitial fibrosis [ci] + tubular atrophy [ct] + chronic vascular changes [cv]; <http://tpis.upmc.edu/tpis/schema/KNCode97.html>); MBChS, modified Banff chronicity score (glomerulosclerosis [gs] + ci + ct + cv; gs: 0, no global gs; 1, up to 25% gs; 2, 26 to 50% gs; 3, >50% gs); CADI, chronic allograft damage index (interstitial inflammation in nonfibrotic areas: 0% = 0, 1 to 25% = 1, 26 to 50% = 2, >50% = 3; interstitial fibrosis: 0% = 0, 1 to 25% = 1, 26 to 50% = 2, >50% = 3; tubular atrophy: 0% = 0, up to 15% = 1, 15 to 30% = 2, >30% = 3; mesangial matrix: 0% = 0, 1 to 25% = 1, 26 to 50% = 2, >50% = 3; gs: 0% = 0, <15% = 1, 16 to 50% = 2, >50% = 3; vascular intimal proliferation: 0% = 0, 1 to 25% = 1, 26 to 50% = 2, >50% = 3).

Posttransplantation Biopsies

Of the subsequent 231 biopsies (164 protocol and 67 clinically indicated), 22 were considered inadequate by Banff criteria. None of the biopsies had viral inclusions, features of diabetic nephropathy, chronic transplant glomerulopathy, or arteriopathy. None of the patients had significant proteinuria, defined as urine protein:creatinine ratio >1. The incidence of hypertension was 24% at 3 and 6 mo and 18% at 12 mo, with 0 and 2% on two or more antihypertensive drugs at 12 and 24 mo after transplantation, respectively. CrCl in steroid-free patients was excellent at 12 and 24 mo, at 89.2 ± 24.8 and 88.2 ± 22.8 ml/min per 1.73 m², respectively.

Biopsies were scored pathologically for the following diagnoses: CNIT, acute rejection, and chronic injury. Biopsies with CNIT were given a CNIT score (developed for this study), and all of the biopsies (including non-CNIT diagnoses) were assessed for chronicity using three established scores: BChS, MBChS, and CADI (12–15).

CNIT

Criteria. Histologic diagnosis of CNIT was based on identifying one or more of the following features in 83 biopsies: Tubular isomeric vacuoles, medial ah, and striped fibrosis (10,18,19). Striped fibrosis was defined as areas of interstitial fibrosis and tubular atrophy alternating with preserved cortex and identified in more than one focus. Among the diagnostic features, tv was seen in 47% of all biopsies with CNIT, arteriolar hyalinosis in 29% of biopsies, and a striped pattern of interstitial fibrosis in 61% of biopsies; two or more of these specific diagnostic features were identified in 34% of biopsies. Arterio-

lar hyalinosis was focal in 24 biopsies (score of 1), with severe multifocal hyalinosis in only four cases. Two patients had sub-endothelial ah on engraftment biopsies. Both patients developed CNIT lesions of medial nodular hyaline in the arterioles on their 3-mo protocol biopsies, distinct from the intimal hyaline that was observed in the engraftment biopsy.

Incidence. CNIT was diagnosed in 35.9% (83 of 231) of all biopsies overall, and 80% of the patients were identified to have features of CNIT (40 of 50 patients) at some point in the study. The incidence of CNIT was higher in protocol over clinically indicated biopsies (41.5% [68 of 164] versus 22% [15 of 67]; *P* < 0.001; Tables 2 and 3), although there was no significant difference in the mean CNIT score between the protocol (3.67) and clinically indicated biopsies (3.07; *P* = 0.15).

Semiquantitative CNIT Score. As mentioned previously, CNIT scoring was performed using the diagnostic features of CNIT while also incorporating chronicity changes (Table 1). The mean CNIT score increased over time after transplantation (from 3.25 at 3 mo to 4.67 at 24 mo), in keeping with accrual of CNIT injury in the face of continuing CNI exposure (Figure 2). As seen in Figure 3, tubular atrophy and interstitial fibrosis contributed the most to the CNIT score. Moreover, the overall mean scores for tubular atrophy and interstitial fibrosis are similar, suggesting a similar/parallel pathway of injury. At 2 yr after transplantation, arteriolar hyalinosis seems to be the most important contributor to the CNIT score. Only three patients had mesangial matrix increase, but all had evidence of recurrent glomerulonephritis and therefore were not scored.

Acute Rejection

A diagnosis of acute rejection was made on 11 (8) (4.7% of all biopsies) biopsies from nine patients, with six biopsies being clinically indicated and three protocol (subclinical acute rejection at 1.8%; Tables 2 and 3). In some cases, multiple biopsies were obtained from the same patients for monitoring the resolution of acute rejection. At 2 yr, patient incidence of clinical acute rejection was 8% (four patients) and subclinical acute rejection was 10% (five patients).

Table 2. Pathologic diagnoses for protocol and clinically indicated biopsies^a

Biopsy Diagnosis	n	% Biopsies
CNIT ^b	82	35.5
CAN	87	38
Acute rejection ^b	10	4.3
Acute rejection + CNIT	1	0.4
No significant abnormality	17	7
Other (ATN, reflux, GN, etc.)	12	5
Inadequate	22	9.5
Total	231	100

^aCAN, chronic allograft nephropathy; ATN, acute tubular necrosis; GN, glomerulonephritis.

^bDoes not include cases with both features of CNIT and acute rejection.

Table 3. Pathologic diagnoses for protocol biopsies (performed in the setting of stable graft function at different time points after transplantation for surveillance)^a

Biopsy Diagnosis	3 Mo	6 Mo	12 Mo	24 Mo	Total	% Biopsies
CNIT ^b	17	18	18	14	67	40.9
CAN	18	15	15	10	58	35.7
Acute rejection ^b	0	1	1	0	2	1.3
Acute rejection + CNIT	0	0	0	1	1	0.6
No significant abnormality	7	2	1	2	12	7.3
Other (reflux, ATN, GN, etc.)	0	1	3	2	6	3.7
Inadequate	4	7	4	3	18	11
Total	46	44	42	32	164	100

^aMore than two thirds of the biopsies have chronic injury from CNIT or other undefined causes of CAN. Fewer than 10% of biopsies are completely normal at 2-yr follow-up.

^bDoes not include cases with both features of CNIT and acute rejection.

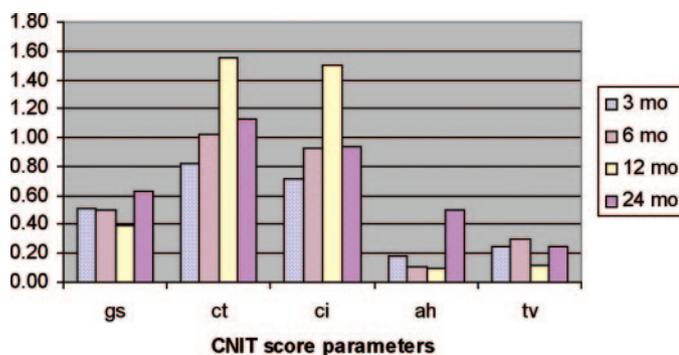


Figure 3. Various parameters of CNIT score at different study points after transplantation. tv, tubular isometric vacuolization.

C4d Staining

There was available additional material for C4d staining on 189 biopsies, and we were able to perform C4d on all biopsies with a diagnosis of acute rejection. Only one clinically indicated biopsy (3.5% of biopsies with acute rejection; Banff IB) had diffuse positive staining along the peritubular capillaries. This acute rejection episode in this patient was steroid resistant and required a prolonged course of Thymoglobulin. No correlation was seen between positive C4d staining and acute rejection or CNIT.

Chronicity Scoring by BChS, MBChS, and CADI Scores

Chronic changes in protocol biopsies, as reflected by the chronicity scores were seen even at 3 mo. Nonspecific interstitial fibrosis was seen in 57% of protocol biopsies at 3 mo, 64% at 6 mo, and 81% at 12 mo. The extent of interstitial fibrosis was milder at 3 mo (ci score of 0.59) but increased subsequently (ci score 0.8 at 6 mo, 1.38 at 12 mo). The tubular atrophy had similar trend. The mean BChS increased progressively from 2.02 at 3 mo to 3.67 at 12 mo, but the score at 24 mo was relatively low at 2.19. The MBChS and CADI showed a similar trend.

Clinical Correlation of Measured Scores

The CNIT, BChS, MBChS, and CADI scores at 3, 6, 12, and 24 mo were correlated with CrCl, proteinuria, tacrolimus levels

and dosage, and number of antihypertensive agents required to normalize BP. On statistical analysis, the CNIT score at 3 mo significantly correlated with 12 mo CrCl ($P = 0.021$, $r^2 = -0.54$) and also 24 mo CrCl ($P = 0.03$, $r^2 = -0.58$; Figure 4). No correlation was seen with number of antihypertensive agents or δ CrCl or proteinuria at 12 and 24 mo. Similarly CADI, BChS, or MBChS showed no correlation with any clinical outcome data. The CNIT score did not correlate with either the tacrolimus level or weight-adjusted dosage at any of the posttransplantation protocol time points. There was cross-correlation between the CNIT score and MBChS for chronicity parameters, because both scores shared three of the studied parameters (gs, ci, ct; $r = 0.79$).

We also compared the tubular atrophy and interstitial fibrosis scores of biopsies with CNIT diagnosis and non-CNIT diagnoses at different time points of 3, 6, 12, and 24 mo. Only the interstitial fibrosis score at 12 mo was significantly higher in CNIT biopsies than in non-CNIT biopsies ($P = 0.04$). No significant differences were seen in the tubular atrophy or interstitial fibrosis scores between these two groups at 3, 6, or 24 mo.

Development of a Clinically Relevant CNIT Scoring Model

On the basis of our results, we created a model for CNIT scoring so as to improve its validity. The various individual parameters were weighted differentially using statistical linear multiple regression models. Because the number of cases analyzed was small on statistical grounds, we reduced the number of parameters to gs, ct, medial ah, and tv (Figure 5). Mesangial matrix increase was excluded because it was not observed in our biopsies, and interstitial fibrosis was excluded because it was more or less similar to ct. The following equation, when used to calculate the CNIT score, improves the correlation with outcome:

$$\text{CNIT model score} = -0.16 + (1.05 \times \text{gs} + 2.05 \times \text{ct} + 0.95 \times \text{ah} + 1.03 \times \text{tv})$$

We tested the validity of this model by identifying a separate validation set of 44 subsequent new patients from our kidney transplantation database with 3-mo protocol biopsies and at least 12 mo of follow-up. On review, 14 patients had a diagnosis of CNIT on 3-mo protocol biopsies. These patients were on

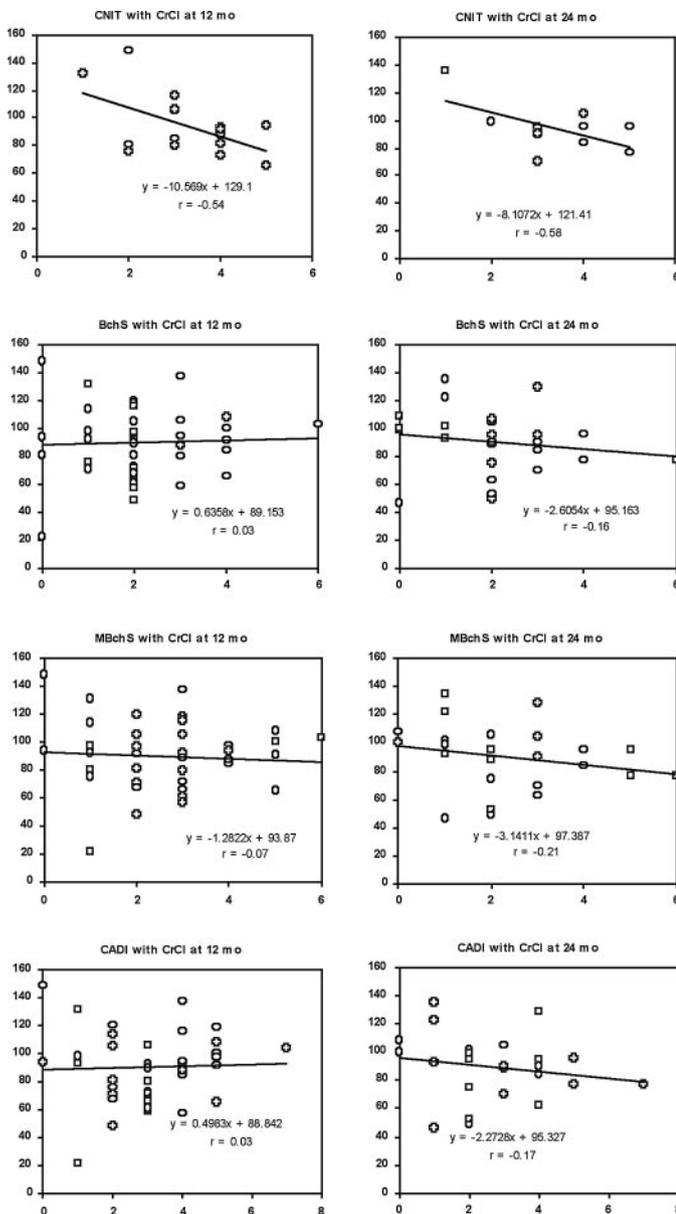


Figure 4. Correlation among CNIT, BChS, MBChS, and CADI scores with creatinine clearance (CrCl) at 12 and 24 mo.

either steroid-based ($n = 3$) or steroid-free ($n = 11$) immunosuppression. Of these, 11 patients had 24 mo of posttransplantation follow-up. The 3-mo biopsies were given a CNIT score, and on the basis of the model, a CNIT model score was calculated and was correlated with CrCl at 12 and 24 mo. The mean CNIT model score was 4.08 (range 1.97 to 9.28). The 3-mo CNIT model score correlated significantly with both 12-mo ($P = 0.02$, $r^2 = -0.54$) and 24 mo ($P = 0.004$, $r^2 = -0.75$) CrCl.

Discussion

The nephrotoxic potential of CNI is widely known, but the results of CNI-sparing regimens have been inconclusive and CNIT may be accepted as a trade-off for better early graft survival (20–22). The utility of a clinically correlated CNIT score would be enormous, because it would serve to predict

Diagnostic features of CNIT	Parameters of CNIT scoring system in biopsies with CNIT	Correlation of CNIT Score with renal function	Development of a Predictive CNIT Model Score*	Validation of CNIT Model Score on independent biopsy set
Tubular isometric vacuoles	Tubular isometric vacuoles	3 month CNIT Score correlates with:	Tubular isometric vacuoles	3 month CNIT Model Score correlates with:
Striped interstitial fibrosis	Tubular atrophy		Tubular atrophy	
Arteriolar medial hyalinosis	Arteriolar medial hyalinosis	12 month CrCl ($p=0.021$)	Arteriolar medial hyalinosis	12 month CrCl ($p=0.02$)
	Glomerulosclerosis	24 month CrCl ($p=0.03$)	Glomerulosclerosis	24 month CrCl ($p=0.004$)
	Interstitial fibrosis			
	Mesangial matrix increase			

Figure 5. Development of CNIT model score. For reducing the number of parameters for analysis, interstitial fibrosis was excluded because the scores were similar to that of tubular atrophy; mesangial matrix increase was seen only in biopsies with recurrent GN.

future clinical graft outcome and provide the trigger for educated therapeutic intervention. In our study, we documented the incidence of CNIT and developed a semiquantitative CNIT scoring system and subsequently a CNIT model score that is useful in predicting the future graft function. Our CNIT scoring system uses chronic injury components of BChS and also incorporates histologic features of acute CNIT. Our patient cohort seems ideal for this study, because all allografts manifested immediate graft function and the incidence of acute rejection was low. At our center, we use strict criteria for acceptance of deceased donor grafts and also greatly minimize cold ischemia time. Therefore, the existence of confounding histologic factors is low.

In our biopsy review, an etiologic categorization of the allograft biopsies is attempted whenever feasible, all the while adhering to strict histologic criteria. The morphologic features described in CNIT are nonspecific at best (4,10,19). However, these changes do offer a glimpse of possible cause in an otherwise default diagnosis of CAN in an allograft biopsy. Availability of day 0 biopsies in at least a subset of our study patients controls for these confounding factors to some extent. We have excluded other possible causes of these histologic features; none of our patients had diabetes, and hypertension was not a significant problem; features of chronic allograft arteriopathy were not seen. Moreover, we scored only biopsies with medial/peripheral ah. Striped pattern of fibrosis was documented only when evident unequivocally; only two biopsies that were diagnosed as CNIT on the basis of striped fibrosis had a previous diagnosis of acute rejection. On the basis of these criteria, 41.5% of protocol biopsies had features of CNIT. Only one biopsy with acute rejection was C4d positive, suggesting that CR was not a significant contributor of CAN in our transplant population (23,24).

Protocol biopsies are invaluable in early detection of structural damage to the allograft (14,25,26). Several scoring systems, such as BChS and CADI, have been developed to measure semiquantitatively chronic changes in the biopsy. Although some of these scores can predict future graft survival (12,14,27,28), others have failed to demonstrate any clinical significance. These chronicity scores identify already estab-

lished chronic tubulointerstitial damage, and none tries to document the possible underlying cause. It also is widely known that individual susceptibility to renal dysfunction is the more likely cause of CNIT, rather than the dosage of tacrolimus itself, underscoring the necessity of protocol biopsies for optimal graft surveillance.

Various studies have suggested that new-onset tubular atrophy and interstitial fibrosis occur in the early posttransplantation period, usually within 3 mo (29,30). On the basis of the chronicity scores, similar findings were observed in our biopsies. Interstitial fibrosis, albeit mild, was seen at 3-mo protocol biopsies and approached 81% of protocol biopsies at 12 mo. In our study group, 90% of the transplantations were from healthy living-related donors (age range 34.13 ± 9.64), without hypertension or diabetes. In addition, only a minor subset of engraftment biopsies showed glomerulosclerosis and chronic tubulointerstitial damage. On the basis of these data, the majority of the chronic changes that were seen in our 3-mo protocol biopsies seem to be of new onset and transplantation related. Of the 23 engraftment biopsies reviewed, only two had ah, which clearly was subendothelial. Hence, ah is presumed to be due to CNIT.

We have documented the clinical validity of the CNIT scoring system and a CNIT model score. On the basis of the longitudinal studies that have documented the features of CNIT, it should be emphasized that our CNIT model score is validated for 3-mo protocol biopsies (3). Although CNIT score and MBChS share several parameters, it is interesting that only CNIT score correlated with renal function. In addition, there were no significant differences in the MBChS in biopsies with a diagnosis of CNIT *versus* non-CNIT at 3, 6, 12, or 24 mo. The unique feature in CNIT scoring may be ah, which increases the validity of the CNIT score. The CNIT score is the only score that increases progressively from 3 to 24 mo, and this seems to be due to a high mean δ (12 to 24 mo) ah score (Figure 3). In our analyses, ah score alone does not correlate with the clinical end points of CrCl or hypertension. Although tubular atrophy and interstitial fibrosis do contribute most to the CNIT score (Figure 3), we have established that the clinical validity of the CNIT score is not due to a selection bias toward biopsies with greater tubular atrophy and interstitial fibrosis. On the basis of these results, ah seems to be the single most important contributor to the CNIT scoring system that drives its clinical validity. It seems that ah is irreversible and, when seen, should not be underestimated.

In the case of CNI-mediated ah, hyaline deposition is probably due to a combination of increased vascular resistance, endothelial injury, and necrosis of smooth muscle cells (4,18,31–34), resulting in the characteristic arteriolar medial distribution (5). The major resistance vessel being the afferent arteriole, it often displays the conspicuous histopathologic alterations. Although the precise mechanism is not known, CNI cause renal vasoconstriction, primarily acting on the afferent arterioles (4,31,35,36). When superimposed hyaline deposition occurs in these arterioles, it might lead to impaired autoregulation, as in aging, hypertension, and diabetes (34,37–39). Autoregulation is a protective mechanism that ensures a constant GFR and prob-

ably is mediated by a combination of afferent arteriolar myogenic reflexes and tubuloglomerular feedback (40). In the presence of hyaline deposition, the afferent arterioles can become pressure-passive conduits, increasing the glomerular vulnerability to both ischemic injury and barotraumas. Similar changes explain the progressive loss of renal function in patients even after discontinuation of the CNI (35,41).

Whereas we and other investigators believe that chronic CNIT leads to progressive renal disease, especially if followed over several years after transplantation (35), others have shown either stable or improvement of graft function after discontinuation of CNI (18,42). It has been suggested that the short-term renal function may be a reflection of whether the renal injury is in the compensated or decompensated stage (35). This reiterates the importance of early detection of chronic CNIT, before the initiation of the final common pathway of progressive renal injury.

The results of our CNIT score on an ongoing steroid-based *versus* steroid-avoidance pediatric kidney transplantation clinical trial will be most helpful in determining whether steroid avoidance has a confounding influence on CNIT biopsy scores. This seems unlikely, though, because the rare protocol biopsy studies in adult renal transplant recipients on steroid-based immunosuppression have shown significantly higher (62%) incidence of “CAN” as a result of tacrolimus nephrotoxicity on 2-yr protocol biopsies (43). The rate of interstitial fibrosis in our biopsies is similar to that reported in another important steroid-based study (2). Additional studies are needed to validate further the CNIT scoring system and also to assess the interobserver agreement and reproducibility.

Conclusion

Although the histologic features of CNIT are not entirely specific, allograft biopsy continues to be the mainstay of a “suggested diagnosis” of CNIT in renal transplantation. In our study, we have shown that ah is a more specific feature of early CNIT injury and may be more important than tubular atrophy and interstitial fibrosis in suggesting progression of renal injury. It therefore would be of great value to be able to detect CNIT before the diagnostic feature of ah sets in. Recent advances in genomics and proteomics, combined with quantitative injury scoring, may offer new molecular markers to understand the early injury mechanisms of CNIT.

Disclosures

None.

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