The Progression of Interstitial Fibrosis and Tubular Atrophy at 6 Months Is an Independent Predictor of Poor Graft Outcomes in Kidney Transplant Recipients

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Background. Interstitial fibrosis and tubular atrophy (IFTA) found on 1-y surveillance biopsies has been associated with poor graft outcomes. However, its progression over time and relationship to outcomes are less well defined. Methods. We studied implantation and 6-mo surveillance biopsies and examined the association between the progression of IFTA (ΔIFTA) and a composite of censored graft loss or doubling of serum creatinine in 248 adult kidney recipients. Results. The percentage of patients with ΔIFTA of 1 or ≥2 was 35% and 22%, respectively. Positive ΔIFTA was a risk factor for the composite endpoint (hazard ratio, 1.36; 95% confidence interval, 1.03-1.79). This estimate was robust to adjustment for recipient and donor baseline characteristics, baseline IFTA, tacrolimus levels, and rejection status. ΔIFTA was associated with decreased estimated glomerular filtration rate at 3 and 5 y. ΔIFTA+i was a predictor in the cohort; however, IFTA progression was not limited to those with a mononuclear cell interstitial inflammation (Banff “i”) score above zero. Notably, donor age was a predictor of IFTA at 6 mo, but not of ΔIFTA, whereas rejection, donor diabetes, and recipient smoking status were. Conclusions. Progression of IFTA at 6 mo can predict outcomes. ΔIFTA was not related to donor age but may be linked to other risk factors influencing decision-making for donor versus recipient selection.

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INTRODUCTION

The role of surveillance kidney allograft biopsies remains controversial.1,2 According to a recent surveys, only 17% of US centers and 28% of Canadian transplant nephrologists use surveillance biopsies for monitoring of allografts.3,4 Although they are more costly and risky than follow-up by peripheral blood sampling, the procedure is relatively safe with a reported complication rate of <3 of 1000 cases of serious bleeding requiring transfusion or direct intervention.1 Surveillance biopsies are not the only surveillance tool for which there is a paucity of evidence-based benefit; common markers used in follow-up such as serum creatinine levels have been shown to be poor predictors of graft loss despite being strong risk factors.5,6 Instead, the best predictor of allograft function is persistent inflammation of any type shown via biopsy at 1 y postoperatively.5,9 Acute rejection is not the only information that can be gained from a protocol biopsy. In addition, chronic tubulo-interstitial changes can indicate ongoing graft parenchymal loss that has not yet translated into detectable changes in serum creatinine or proteinuria. Using a single time point of surveillance at 1 y posttransplantation, previous studies have demonstrated that a combination of inflammation and fibrosis can predict long-term allograft survival, whereas fibrosis alone does not.10,11 However, the lack of association between cross-sectional assessment of fibrosis and outcome may be confounded by the level of fibrosis at time of transplant.
This may be particularly true in the current era of increased use of marginal kidneys. A given level of fibrosis in a kidney procured from a marginal donor that has a high level of fibrosis at implantation that then remains stable may not have the same prognostic impact as the same level fibrosis in a kidney procured from a healthy young donor who shows no fibrosis at implantation.

In a previous study conducted in the cyclosporine era, a delta analysis on 99 kidney-pancreas recipients who had at least 3 protocol biopsies obtained up to 10 y posttransplant showed IFTA to increase primarily in the first year. Other studies have shown some correlation between estimated glomerular filtration rate (eGFR) and the progression of chronic allograft nephropathy between biopsy at implantation and at varying time points for up to 12 mo. However, to our knowledge, no studies have assessed IFTA progression as a predictor for a longer period. We hypothesized that progression of IFTA from implantation biopsy and early surveillance biopsy at 6 mo would be predictive of graft outcomes.

MATERIALS AND METHODS

Study Design and Population

This was single-center, observational, retrospective cohort study of unsensitized patients who received implantation, and 6-mo surveillance biopsies between September 2011 and September 2020. The implantation biopsy protocol began in September 2011 and became systematic in April 2013. During this period, all patients were offered the 6-mo biopsy. Patients were excluded if they did not receive both the implantation and the 6-mo surveillance biopsy. During this period, the decision to perform an indication rather than a surveillance biopsy was individualized but was generally triggered by an increase of serum creatinine of 25% without obvious cause or an increase in proteinuria equivalent to 0.5 g/d. The clinical follow-up was conducted until March 2021. No patients were lost to follow-up. The study was approved by the institutional ethics committee (GU13-111). The reported clinical and research activities were conducted following the Principles of the Declaration of Istanbul.

Immunosuppression

The induction is described in Table 1 and was followed by maintenance of tacrolimus, mycophenolate mofetil, and steroids. Rejection, subclinical rejection, and borderline rejection were treated with methylprednisolone pulses (200 mg) for 3 days followed by prednisone tapering (0.8 mg/kg per day, reduced by 5 mg per day until return to baseline dose) administered under the treating physician. Thymoglobulin was administered to patients with T cell–mediated rejection under the supervision of the transplant nephrologist.

Histological and HLA Antibody Assessment

Biopsies were prospectively graded by local attending renal pathologists (E.L. and J.R.) according to the Banff 1997 criteria and their subsequent updates. The addition of the individual scores from 0 to 3 for interstitial fibrosis (ci score) and tubular atrophy (ct score) was used to calculate the interstitial fibrosis/tubular atrophy (IFTA) score. The variation in IFTA scores (ΔIFTA) between month 6 and month 0 was then calculated by subtracting IFTA score at implantation from IFTA score at 6 mo. All biopsies were reviewed with a complete team of pathologists and nephrologists during weekly clinical-pathologic transplant conferences where challenging cases were discussed. Patients were screened pretransplant for anti-HLA antibodies using FlowPRA beads. Whenever antibody screening was positive, samples were tested for anti-HLA antibody identification using Luminex single antigen beads since 2012. During the study period, kidney allocation was limited to patients who had a negative virtual crossmatch on cumulative historical and current sera and a negative cytotoxicity crossmatch. For further safety, flow crossmatch was also performed for patients who had calculated panel-reactive antibody above 80% and the kidney offer was refused if this crossmatch was positive.

Definition of Outcomes

The primary outcome was a combination of death-censored graft failure or doubling of the serum creatinine level, defined as a persistent doubling from the level recorded on the day of the protocol biopsy.
Statistical Analyses

The relationship between ΔIFTA and the composite endpoint was assessed by the Kaplan-Meier method, the log rank test, and the Cox proportional hazards model. Average tacrolimus levels were computed by calculating the mean of the values obtained monthly between months 12 and 60 post-transplant. Multivariable linear regression models were used to analyze the association between ΔIFTA and the ΔeGFR at 3 and 5 y compared with the 1-y value. For this analysis, an eGFR value of 5 mL/min was imputed for each time point following graft loss in subjects with failed grafts. Statistical analyses were performed using STATA version 11.0 (StataCorp, College Station, TX) and SPSS Statistics version 26 (IBM, Armonk, NY). All tests were 2-tailed, and a P < 0.05 was considered statistically significant.

RESULTS

Study Population

A total of 486 patients were transplanted during the study period. From the 402 patients with adequate implantation biopsies, 68 were excluded because they failed to undergo the 6-mo protocol biopsy; this failure was due to patient refusal, patients residing in a remote area, anticoagulation, or technical challenges related to posttransplant complications. A total of 86 patients underwent indication biopsies within a month of the 6-mo time point and were also excluded. Thus, the study ultimately included 248 patients; these were mostly male, White, or recipients of a first transplant from a deceased donor or had a mean age of 51 y (Table 1). Two patients had de novo donor-specific antibodies (DSAs) before the surveillance biopsy.

IFTA at Baseline and Variation at 6 Mo

On implantation biopsy, 25 (10.1%) patients were without chronic tubulo-interstitial lesions, 108 (43.5%) had IFTA scores of 1, 101 (40.7%) patients had scores of 2, and 14 (5.6%) had scores of 3 or higher (Figure 1A). When 6-mo biopsies were compared with the implantation biopsies, 99 (39.9%) patients had no variation in their IFTA score, whereas 5 (2.0%) and 2 (0.8%) had scores lowered by 1 and 2 points, respectively. Over a third of the cohort had ΔIFTAs of 1 (87, 35.1%), and 55 patients (22.2%) had ΔIFTAs ≥2 (Figure 1B).

Making statistical inferences about the correlation between IFTA and ΔIFTA is limited by the design of the Banff scoring system, in which the IFTA is capped at a value of 6. Therefore, the distribution of possible values of ΔIFTA differs for each baseline score. For instance, patients with a baseline IFTA of zero can have ΔIFTA from 0 to 6, whereas those with a baseline IFTA of 4 have ΔIFTA distribution limited from 0 to 2. In this context, we first dissected the histogram in Figure 1A by depicting for each baseline IFTA value the detailed distribution of ΔIFTA (Figure 1C). This figure shows that the progression was not limited to those who had high scores at implantation. Second, we conducted a similar analysis in which we examined the IFTA scores at 6 mo according to the baseline IFTA values. Figure 1D shows that high values at 6 mo were found for each baseline IFTA values. Taken together, these data indicate that the positive ΔIFTA and high IFTA at 6 mo were not limited to patients with high levels at baseline.

Association Between ΔIFTA and Graft Outcomes

The median follow-up time was 49 mo (25th–75th percentiles, 36–68 mo). During the study period, 27 (11%) patients suffered graft loss censored for death or doubling of serum
creatinine, at a median of 29 (16–42) mo. To verify whether ΔIFTA predicted the occurrence of this composite endpoint, we first conducted a survival analysis using ΔIFTA as a continuous variable. The raw analysis revealed that each increase in 1 unit of ΔIFTA associated with a 3.6-fold risk of the endpoint (95% confidence interval [CI], 1.03-1.79; P = 0.032; Table 2). This estimate was robust to adjustment for recipient baseline characteristics, delayed graft function, ischemia times, donor characteristics, donor type, donor eGFR, and DSA status. Further adjustment for IFTA score at implantation resulted in a stronger association, which remained similar when mean tacrolimus levels were added to the model (hazard ratio [HR], 1.53; 95% CI, 1.07-2.17; P = 0.018).

Using IFTA values as a continuous variable in a survival model has some limitations because it is a semiquantitative score. We thus conducted an analysis in which we first categorized the ΔIFTA values using cutoff points at 1 and 3 (Figure 2A). The threshold of ΔIFTA > 3 was associated with a poor outcome. However, only 11 (4.4%) patients fell into this group. Second, we examined the occurrence of the composite endpoint for each single value of ΔIFTA score increase up to ≥3. As seen in the Kaplan-Meier curves in Figure 2B, there was a gradual increase in risk with each increment of the ΔIFTA category. The percentages of patients experiencing the endpoint for each of these categories are displayed in Figure 2C, whereas the proportional hazards model shown in Figure 2D shows the quantification of risk by adjusted HRs. These results indicate a calibrated accentuation in the risk of reaching the composite endpoint when ΔIFTA increases.

Association Between ΔIFTA and Graft Function Over Time

The eGFR up to 5 y posttransplant according to the ΔIFTA categorized as ≤0, 1, 2, and ≥3 is displayed in Figure 2E. Analyzed as cross-sectional values, there was a nonsignificant difference in eGFR between groups at 1 y (mean ± SEM 57 ± 2, 60 ± 2, 51 ± 2, and 53 ± 4 mL/min respectively, P = 0.07 by ANOVA) and 5 y (56 ± 3, 59 ± 4, 45 ± 6, and 44 ± 7 mL/min, respectively, P = 0.11 by ANOVA). Multivariable regression models revealed that for each increase of 1 unit of ΔIFTA, there was a significant reduction in eGFR of 2.1 mL/min at 3 y and of 3.3 mL/min at 5 y (Table 3).

IFTA Progression and Rejection or BK Nephropathy

We next questioned whether the progression of IFTA was not essentially a lesion in the path between rejection or BK virus nephropathy (BKVN) and the adverse graft outcome. Nine patients (4%) in the cohort had biopsy-proven rejection or BKVN before the 6-mo protocol biopsy, a proportion consistent with the OPTN 2020 Report indicating an incidence of <7% acute rejection rate by 1 y posttransplant.22 A total of 59 patients had subclinical lesions at 6 mo characterized by borderline changes suspicious for T cell–mediated rejection (minimum t11)23 or acute lesions in the spectra of antibody-mediated rejection (g > 0, ptc > 0, v > 0, C4dIH > 0, C4dIF ≥ 2). We compared these 68 patients to those with no such lesions (n = 180). IFTA progression was observed in both groups, albeit with a slightly different distribution; the patients with signs of rejection had a higher proportion of ΔIFTA ≥3 (P < 0.01 by chi-square test; Figure 3A). When the rejection and BKVN statuses were added to the survival analysis, the association between ΔIFTA and the composite outcome remained significant and of similar magnitude to the prior models above (HR, 1.49; 95% CI, 1.06-2.10; P = 0.022). These data indicate that IFTA progression was not limited to patients who presented lesions of acute rejection or BKVN and its effect was independent of these 2 events.

ΔIFTA and Inflammation

A previous analysis of 1-y protocol biopsies by Cosio et al compared patients with “favorable” versus “unfavorable” histology based on ci and i scores, signs of chronic or active antibody-mediated rejection, and glomerular disease.24 We used this exact classification and examined the composite endpoint in this study’s cohort (Figure 3B). There was only 1 patient in the “positive Banff “i” score (above zero) but negative ci score and no signs of glomerulonephritis” category, so this group is not presented. Consistent with the data reported by Cosio et al, we found no events in patients with minor changes (ci = 0 and i = 0), a low number of events in “favorable” patients with mild IFTA (ci = 1 and i = 0, 9/117, 7.6%), but a large number of events in those with moderate-to-severe IFTA (ci = 2-3 and i = 0, 9/47, 19.1%) and IFTA+i (ci > 0 and i > 0, 4/21, 19.0%), considered “unfavorable.” To further analyze the impact of inflammation, we compared the distribution of ΔIFTA in patients with an “i” score of zero (n = 221) or above zero (n = 27). Higher ΔIFTA was more frequent in those with inflammation (P < 0.01 by chi-square test; Figure 3C), but was not limited to patients with inflammation. Adding the “i” score to the model instead of the rejection and BKVN statuses resulted in similar estimates (HR, 1.50; 95% CI, 1.03-2.19; P = 0.036).

Predictors of ΔIFTA

Finally, we examined potential predictors of ΔIFTA. To this end, we included in the multivariable linear regression an extended list of recipient and donor data, including past medical history characteristics (Table S1, SDC, http://links.lww.com/TXD/A447). The significant predictors were the following: donor diabetes (β = 1.48 ± 0.55, P = 0.01), recipient past or current smoking (β = 0.44 ± 0.19, P = 0.02), and biopsy-proven acute rejection, subclinical rejection, or BKVN (β = 0.64 ± 0.22, P < 0.01). Other predictors that had a P value above 0.05 but below 0.10 included DGF (β = 0.55 ± 0.29, P = 0.06), peripheral arterial disease (β = 0.44 ± 0.26, P = 0.09), and positive DSA (β = 1.48 ± 0.90, P = 0.10).

DISCUSSION

In this report, we showed that the progression of IFTA seen on surveillance biopsies between implantation and 6 mo...
posttransplant predicted lower graft function at 5 y along with a higher likelihood of composite of graft loss and doubling of serum creatinine levels. The prediction was independent of recipient and donor baseline characteristics, baseline IFTA, and tacrolimus through levels. The increase in IFTA occurred in patients with and without evidence of rejection or BKVN, showing that these events are important but not essential to progression.

Protocol biopsies have been key to improving the understanding of the pathophysiology of graft failure; however, a question that remains is whether or not chronic tubulo-interstitial lesions in the absence of inflammation within the
The assessment of interstitial inflammation has become more complex since the first Banff consensus. The most recent addition to the Banff scoring system is the i-IFTA score, which started to be routinely evaluated following publication of the 2015 Banff report. As stated by Nankivell “The i-IFTA pattern is not synonymous with the total inflammation (ti) score (counting total cortical inflammation) or the Boolean combination of Banff i inflammation occurring with IF/TA (“i+IF/TA”).” The classification will most likely continue to evolve as the prognostic impact of each of these inflammation scores and their interaction becomes clearer. Nonetheless, the IFTA per se remains one of the key elements considered by clinicians when making the decision of therapeutic aggressiveness in the face of rejection, disease recurrence, and so on. The current study shows the usefulness, for centers that perform longitudinal surveillance biopsies, of monitoring not only the IFTA on an ad hoc basis but also its evolution over time.

Cosio et al reported a large cross-sectional study of >900 biopsies performed at 1 y in which they examined the impact of mild and moderate-to-severe IFTA without inflammation on graft outcomes. This analysis showed that patients with ci scores of 2 or 3 or ci scores of at least 1 combined with i scores of at least 1 (termed IFTA+i) had an unfavorable outcome. The study population here used more recent transplantations and

| TABLE 3. Univariate and multivariate beta coefficients for ΔIFTA associated with ΔeGFR at 3 y and 5 y post transplant |
|------------------------|------------------------|------------------------|------------------------|
| 3 y (n = 197) | 5 y (n = 106) |
| β (95% CI) | P | β (95% CI) | P |
| Δ IFTA (continuous) | Unadjusted | –1.8 (–3.0 to –0.4) | 0.011 | –2.7 (–5.2 to –0.2) | 0.036 |
| | Adjusted model 1 | –2.1 (–3.4 to –0.7) | 0.003 | –2.5 (–3.3 to –0.3) | 0.085 |
| | Adjusted model 2 | –2.1 (–3.6 to –0.6) | 0.008 | –3.2 (–3.0 to –0.2) | 0.039 |
| | Adjusted model 3 | –2.1 (–3.6 to –0.5) | 0.008 | –3.3 (–3.4 to –0.2) | 0.038 |

1 Adjusted for recipient age and sex, delayed graft function, warm ischemia time, cold ischemia time, donor age and sex, donor type, donor estimated glomerular filtration rate, and DSA.

2 Adjusted for above plus IFTA score at implantation.

3 Adjusted for above plus average tacrolimus trough levels.

DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; IFTA, interstitial fibrosis and tubular atrophy.

FIGURE 3. Distribution of ΔIFTA scores according to the rejection status (A) Percentage of patients in each category of ΔIFTA following stratification by the presence or absence of biopsy-proven rejection, lesions suspicious of rejection or BKVN. (B) Kaplan-Meier plots and log rank test of the composite endpoint by the classification described by Cosio et al: minor changes (ci0, i0), i > 0 without ci or glomerulonephritis, IFTA (ci1, i0), IFTA + i (ci > 0, i > 0), cAMR (cg > 0 or g+ptc ≥ 2), glomerulonephritis other than transplant glomerulopathy. (C) Percentage of patients in each category of ΔIFTA following stratification by the presence or absence of inflammation (i = 0 vs i > 0) on the surveillance biopsy. BKVN, BK virus nephropathy; IFTA, interstitial fibrosis and tubular atrophy.
suggested that control of inflammation would help to slow the IFTA progression, but causality obviously cannot be inferred from the associations above. A previous trial did not show benefit of early treatment of acute rejection (before 6 mo) diagnosed by surveillance biopsies on the IFTA progression at 6 mo.2 These data and our analysis suggest that other factors, unrelated to inflammation, may play an important role in IFTA progression and its unfavorable effect on clinical outcomes.

In fact, the analysis of IFTA progression over time conducted here revealed both similar and different predictors than previous single time point analyses. Classically recognized risk factors in early protocol biopsies include donor age, DGF, and severe and subclinical rejection.7,8,13 In the present population, all these factors were associated with increased ΔIFTA, except for donor age. This observation may suggest that this variable does not trigger per se accelerated injury, or at least does not during the early times posttransplant. In addition to the above factors, donor diabetes and recipient smoking status were significantly associated with an increase in IFTA.

This study had some limitations. There was a substantial proportion of patients who did not undergo protocol biopsy. This is partly explained by the fact that approximately half of the cohort at our center lived in a remote area at the time of study. Because we performed protocol biopsies as an ambulatory procedure, patients from remote areas were often more reluctant than others to delay their return home to accommodate the monitoring period postbiopsy. The routine use of a 6-mo surveillance biopsy may also have inflated the proportion of indication biopsies requested by the transplant physicians. Given that this was a usual time point in our practice to obtain histological assessment, patients who would otherwise have been observed until next serum creatinine controls may have been more likely to be biopsied immediately around 6 mo posttransplant. In all, these limitations may have limited the size of the study population but had likely no impact on the estimates. The i-IFTA score was not available for all patients in this retrospective cohort. Therefore, the impact of inflammation in the areas of fibrosis was not analyzed. Finally, the variation in pathology reads, the sampling limitations, and the inclusion of scarred areas are all intrinsic factors that may limit the generalization of the results.

In summary, our findings revealed that the progression of chronic tubulo-interstitial lesions seen on 6-mo surveillance biopsies was associated with poorer graft outcomes. A randomized clinical trial would be needed to confirm the benefit of surveillance biopsies. Nevertheless, the observational results obtained here confirm that they provide useful prognostic information, which can potentially lead to closer invasive and noninvasive follow-up, to a review of the intensity of immunosuppression, and to questioning the patient’s compliance. For patients with longitudinal follow-up biopsies, subsequent studies may lead to identifying factors that can be modified or avoided to optimize transplant outcomes.

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