Collapsing and non-collapsing focal segmental glomerulosclerosis in kidney transplants

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Abstract

Background. The aetiological and clinical associations of collapsing focal segmental glomerulosclerosis (cFSGS) following kidney transplantation (KTx) are poorly described. In this study, post-transplant cFSGS and non-collapsing FSGS (ncFSGS) were compared in recent KTx recipients. Evidence for intragraft viral infection was sought.

Methods. Twenty-nine cases of post-KTx FSGS were identified and classified as cFSGS (n = 10) or ncFSGS (n = 19). Biopsies were scored using Banff '97 criteria and subjected to in situ hybridization (ISH) for parvovirus B19 (pvB19), simian virus 40 (SV40) and BK virus (BKV).

Results. cFSGS and ncFSGS patients were comparable for age, gender, weight, delayed function, human leucocyte antigen (HLA) matching, acute rejection and median time to diagnosis. Deceased donor source was more common among cFSGS cases (70 vs 32%, P = 0.05). FSGS was recurrent in 2/10 cFSGS cases compared with 8/19 ncFSGS (P = NS). FSGS was associated with more proteinuria (11.9 vs 7.2 g/day, P = 0.05) and higher serum creatinine (4.2 vs 1.9 mg/dl, P = 0.0001) at diagnosis. Plasmapheresis was used in two out of 10 cFSGS and seven out of 19 ncFSGS cases with treatment response in 0 of two and three of seven, respectively. Graft loss was more rapid with cFSGS compared with ncFSGS (P = 0.02). Histologically, cFSGS was associated with more severe chronic vascular abnormalities. All biopsies were negative for pvB19, SV40 and BKV by ISH.

Conclusions. cFSGS following KTx presents with higher proteinuria, diminished renal function, more severe vascular disease and higher rate of graft loss compared with the non-collapsing form. There was no evidence for infection by pvB19 or polyomaviruses.

Keywords: BK virus; focal segmental glomerulosclerosis; kidney transplantation; nephrotic syndrome; parvovirus B19; SV40 virus

Introduction

Collapsing focal segmental glomerulosclerosis (cFSGS) is a histologically defined variant of FSGS characterized clinically by heavy proteinuria, progressive renal insufficiency and rapid evolution to end-stage renal disease (ESRD) [1]. While human deficiency virus (HIV) nephropathy is the most commonly recognized cause, non-HIV-associated cFSGS is well described in native as well as transplanted kidneys [2,3]. Although, existing case series of cFSGS in kidney transplant (KTx) recipients suggest that it can present as a recurrent or de novo disease process and is associated with overall poor prognosis [3,4], there has been little comparison of cFSGS with the non-collapsing form of FSGS (ncFSGS) in the post-KTx setting and reports of treatment outcome for post-KTx FSGS have not typically distinguished the two variants.

The possibility of a viral aetiology for non-HIV-associated cFSGS has been raised by data from a number of studies. An association between parvovirus B19 (pvB19) and cFSGS was suggested by Tanawattanacharoen et al. [5] who demonstrated pvB19 DNA by polymerase chain reaction (PCR) in the majority of renal biopsies from patients with native kidney FSGS as well as those with other forms of primary glomerular disease. In a subsequent study, pvB19 DNA was identified in 78% of native kidney biopsies with cFSGS compared with only 22% of those with ncFSGS. The higher frequency of pvB19 DNA was noted not only in native kidney biopsies, but also in peripheral blood of patients with cFSGS [6]. Finally, a recent report which showed that the eradication of pvB19 with intravenous immunoglobulin therapy was...
associated with recurrence-free re-transplantation further supported its role in cFSGS [7]. Given this accumulating literature and the well-documented association of pVB19 infection with aplastic anaemia in immunosuppressed KTxs recipients [8], it is plausible that intra graft infection with this virus may participate in the pathogenesis of FSGS in the post-transplant setting.

A second viral species—Simian Virus 40 (SV40)—has been similarly implicated in the causation of FSGS. SV40 DNA was identified in 56% of renal biopsies in patients with FSGS [9], although this finding was not confirmed by another, smaller study of the native kidney disease [10]. Nonetheless, the association of other polyomavirus species (BK and JC viruses) with organ-specific disease in the immunocompromised host suggests that SV40-related glomerular disease merits consideration in KTxs recipients with biopsy-proven FSGS [11].

We present here results of a comparative study of cFSGS and ncFSGS among recently transplanted renal allograft recipients which confirms that cFSGS represents a clinically and histologically more severe disease and provides evidence against the involvement of PV B 19, SV40 and BKV in the aetiology of this condition.

**Methods**

**Case identification and histological analysis**

All patients with histological evidence of FSGS on a renal allograft biopsy carried out between 1 January 1994 and 31 December 2003 were identified from the renal biopsy database at Mayo Clinic, Rochester. The biopsies consisted of serial sections prepared on 10 slides—four stained with haematoxylin and eosin (H&E, levels 2, 4, 6 and 7), two with periodic acid-Schiff (PAS, levels 3 and 8), two with methenamine silver stain (levels 1 and 10), and two with Masson’s trichrome stain (MT, levels 5 and 9). Biopsy slides were reviewed by a consultant renal pathologist (D.J.L.) who confirmed the diagnosis of FSGS, classified each case as collapsing or non-collapsing variant, and scored acute and chronic abnormalities according to Banff ‘97 criteria [12]. The Banff scores utilized for this study were as follows: acute interstitial infiltrate (i), acute tubulitis (t), acute glomerulitis (g), acute vasculitis (v), chronic interstitial fibrosis (ct), chronic tubular atrophy (ct), chronic visceral intimal thickening (cv), arteriolar hyalinosis (ah).

Histological criteria for the diagnosis of FSGS included segmental sclerosis of glomerular capillaries with associated hyaline and/or lipid deposition and with variable prominence of overlying visceral epithelial cells and segmental adhesion to a mildly thickened Bowman capsule. The collapsing variant of FSGS (cFSGS) was defined by wrinkling and retraction of the glomerular capillary wall with marked hyperplasia and hyper trophy of the overlying visceral epithelial cells often accompanied by prominent intracytoplasmic protein reabsorption droplets. A diagnosis of cFSGS was made if at least one glomerulus demonstrated these typical changes. Cases with evidence of additional glomerular disease (immune complex-mediated glomerulonephritis, necrotizing glomerulonephritis and transplant glomerulopathy) were not included in the study cohort.

Pertinent pre- and post-transplant clinical and laboratory data and relevant kidney donor information were abstracted from patient medical records with institutional review board (IRB) approval. Time to occurrence of FSGS was defined as the interval between transplantation and initial biopsy diagnosis. Cases were designated as recurrent FSGS if there was biopsy-proven native kidney FSGS clearly documented prior to transplantation. Acute rejection was defined as biopsy-proven acute cellular or humoral (antibody-mediated) rejection prior to the diagnosis of FSGS. Time to graft loss was defined as the interval between biopsy diagnosis of FSGS and return to dialysis. Response to plasmapheresis therapy was defined as 50% or greater reduction in urine protein excretion following initiation of a course of plasmapheresis.

In situ hybridization for parvovirus B19 and SV40

Fresh, 4 μm sections were cut from formalin-fixed paraffin-embedded renal allograft biopsies. The following probes were used for in situ hybridization (ISH): (i) SV40 and BK viruses: biotinylated plasmid containing the entire viral genome (purchased from Enzo Diagnostics, Inc. Farmingdale, NY), and (ii) parvovirus B19: PYT104-C plasmid containing the B19-Au genome [provided by Dr P. Tattersall, Yale University, and labelled with digoxigenin-dUTP (Roche Applied Science, Indianapolis, IN) by nick translation]. After deparaffinization and rehydration, sections were rinsed twice in diethyl pyrocarbonate-treated H2O for 2 min each. Endogenous alkaline phosphatase activity was quenched with 0.2 M HCl for 20 min at room temperature, and slides were microwaved for 10 min in 10 mM citric acid (pH 6.0) and cooled down to room temperature. Sections were then digested with 25 μg/ml proteinase K in 10 mM phosphate-buffered saline (pH 7.2) for 10 min at room temperature, followed by acetylation for 15 min with freshly prepared 0.6% acetic anhydride in 0.1 M triethanolamine (pH 8.0). Pre-hybridization was performed for 30 min at room temperature with a mixture containing 50% deionized formamide, 10% dextran sulfate, 1 x Denhardt’s solution, 3 x standard saline citrate, 100 μg/ml salmon sperm deoxyribonucleic acid, 125 μg/ml yeast transfer RNA, 10 μg/ml polyadenylic-cytidylic acid, 0.05 M Tris, 5 mM ethylenediamine tetra-acetic acid, 600 mM NaCl and 0.1% inorganic sodium pyrophosphate. After the slides were pre-hybridized in pre-hybridization buffer for 10 min, residual pre-hybridization buffer was removed thoroughly from around the tissue section. Biotin-labelled SV40 and BKV DNA probes or digoxigenin-labelled parvovirus B19 DNA probe (1 ng/μl in pre-hybridization buffer) were applied to sections, respectively. Biotin-labelled hepatitis B DNA probe was used for negative control. Slides were covered with a sigmacoatTM-coated cover glass, denatured at 95°C for 5 min and hybridized in a humid environment for 3 h at 50°C. Sections were rinsed twice in 2 x standard saline citrate for 10 min at room temperature, washed in 0.5 x standard saline citrate at 37°C for 20 min (to remove excess probe) and rinsed twice in buffer A for 2 min at room temperature. Sections were blocked for 10 min in blocking buffer A (1% normal swine serum and 0.3% Triton X-100). Digoxigenin-labelled parvovirus B19 DNA probes were detected with anti-digoxigenin-alkaline phosphatase conjugate. The sections were incubated in a 1:200 dilution of alkaline phosphatase-conjugated anti-digoxigenin...
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Fab fragment, in blocking buffer A, for 30 min at room temperature. The biotinylated SV40 and BKV DNA probes were detected using streptavidin conjugated with alkaline phosphatase at a 1:100 dilution (Roche) and incubated at room temperature for 30 min. Rinsing with buffer A and buffer C (Tris HCl and MgCl; pH, 9.5) was performed, and sections were subsequently reacted with nitroblue-tetrazo-lium chloride and 5-bromo-4-chloro-3-indolylphosphate, forming an insoluble blue precipitate at the site of reaction. Sections were then rinsed in buffer C, counterstained with 0.1% Nuclear Fast Red, rinsed again in buffer C, dehydrated in graded ethanol and cleared in xylene, and coverslips were applied with a xylene-based synthetic mounting medium. Positive control tissues included placenta and lung from a patient with pvB19 infection, an SV40-infected human cell line (HP75), and kidney tissue from a patient with BK infection. Negative controls consisted of substituting a hepatitis A DNA probe for the test probe.

Statistical analysis

Comparisons between groups were carried out using the Fisher’s exact test for categorical values and Mann–Whitney U test for continuous variables (JMP 5.1, SAS Institute). Kaplan–Meier analysis and log-rank test were used to compare graft survival between the two groups. Statistical significance was assigned to P-value of ≥0.05.

Results

Demographic and pre-transplant clinical data

A total of 29 cases of biopsy-proven post-transplant FSGS were identified between 1994 and 2003. Of these, 10 were classified as cFSGS and 19 as ncFSGS. Both the groups were predominantly male. Gender distribution, race, body weight, frequency of diabetes mellitus and frequency of dialysis therapy pre-transplant were comparable for the two groups (Table 1). None of the patients in either group had clinical or laboratory evidence of HIV infection. Deceased donor source was more frequent among cFSGS cases compared with ncFSGS (7/10 vs 6/19, P = 0.05). There were no differences between cFSGS and ncFSGS cases for mean number of HLA matches and panel-reactive antibodies. Although pre-transplant nephrotic syndrome was documented in similar proportions of the two groups (3/10 vs 5/19), only two of 10 cFSGS patients had biopsy-proven native kidney FSGS compared with eight of 19 ncFSGS patients (P = 0.075). The median time to FSGS diagnosis was 2.0 years (range 0.1–6.0 years) for the overall group of 10 patients with recurrent disease compared with 1.7 years (range 0.3–10 years) for the remaining 19 patients with apparent de novo post-KTx FSGS (P = 0.06). No patient with biopsy-proven FSGS prior to transplantation had histological features of collapsing variant on native kidney biopsy. Among those with de novo post-KTx FSGS, the aetiology of native kidney disease was variable. In the cFSGS group, it included reflux nephropathy (n = 2), diabetic nephropathy (n = 3), IgA nephropathy (n = 1) and unknown (n = 2). In the ncFSGS, it included diabetes (n = 2), hypertension (n = 1), reflux nephropathy (n = 2), IgA nephropathy (n = 1) and unknown (n = 5).

Post-transplant clinical data

As shown in Table 2, the recipients with cFSGS received ciclosporin-based immunosuppression more frequently (5/10 vs 2/18, P = 0.03) and sirolimus-based immunosuppression less frequently (1/10 vs 6/19, P = 0.06) than those in the ncFSGS group. Delayed graft function (DGF) occurred in 4 out of 10 cases in the cFSGS group compared with 6 of 19 in the ncFSGS group (P = 0.7). Prior to the diagnosis of post-KTx FSGS, the frequencies of acute cellular rejection (6/10 vs 13/19, P = 0.7) and acute humoral

| Table 1. Comparison of pre-transplant characteristics for cases of cFSGS and ncFSGS |
|---------------------------------|-------------------------------|----------------|
| Age (years, mean ± SD)         | cFSGS (n = 10)                | ncFSGS (n = 19) | P    |
| African American (n)           | 3.0 ± 2.1                     | 4.5 ± 1.7       | 0.1  |
| Sex (male)                     | 9 of 10                       | 15 of 19        | 0.6  |
| Weight (kg, mean ± SD)         | 94.9 ± 27.7                   | 81.0 ± 23.9     | 0.3  |
| Biopsy-proven native FSGS (n)  | 2 of 10                       | 8 of 19         | 0.08 |
| Nephrotic-range proteinuria (n)| 3 of 10                       | 5 of 19         | 0.3  |
| Pre-transplant dialysis (n)    | 8 of 10                       | 16 of 18        | 0.5  |
| Panel-reactive antibodies (%)  | 0.1                          | 1.0             | 1.0  |
| Deceased donor (n)             | 7 of 10                       | 6 of 19         | 0.05 |
| Number of HLA matches (mean ± SD) | 1.8 ± 1.9                   | 2.0 ± 1.3       | 0.4  |
| Diabetes mellitus (n)          | 3 of 10                       | 4 of 19         | 0.7  |

| Table 2. Comparison of post-transplant clinical data between collapsing and non-collapsing FSGS |
|---------------------------------|-------------------------------|----------------|
| Immunosuppression (prior to FSGS diagnosis) | cFSGS (n = 10)                | ncFSGS (n = 19) | P    |
| CYA*AZA/PRED                    | 5 of 10                       | 2 of 19         | 0.03 |
| TAC/MMF/PRED                    | 3 of 10                       | 10 of 19        | 0.2  |
| MMF/PRED                        | 1 of 10                       | 1 of 19         | 0.5  |
| SRL/MMF/PRED or SRL/PRED        | 1 of 10                       | 6 of 19         | 0.2  |
| Delayed graft function (n)      | 4 of 10                       | 6 of 19         | 0.7  |
| Acute cellular rejection (n)    | 6 of 10                       | 13 of 19        | 0.7  |
| Acute humoral reaction (n)      | 1 of 10                       | 2 of 9          | 1    |
| Time to FSGS (years), median (range) | 1.7 (0.1–10.0)               | 1.0 (0.02–6)    | 0.3  |
| Recurrent FSGS (n)              | 2 of 10                       | 8 of 19         | 0.2  |
| Proteinuria at diagnosis (mg/dl) | 11.9 ± 6.8                   | 7.2 ± 9.5       | 0.04 |
| Serum creatinine at diagnosis (mg/dl) | 4.2 ± 2.6                   | 19.6 ± 0.6     | 0.0001 |
| Plasma pheresis (n)             | 2 of 9                        | 7 of 19         | 0.3  |
| Response to plasma pheresis (n) | 0 of 2                       | 3 of 7          | 0.4  |

*CYA, cyclosporine; AZA, azathioprine; PRED, prednisone; TAC, tacrolimus; MMF, mycophenolate mofetil; SRL, sirolimus.
rejection (1/10 vs 2/19, \( P = 1 \)) were also comparable between the two groups. The median time to diagnosis of FSGS from the date of transplantation was 1.5 years (range 0.1–10 years) for cFSGS and 1.0 years (range 0.02–6 years) for ncFSGS (\( P = 0.7 \)). FSGS was recurrent in two of 10 cases of cFSGS compared with 8 of 19 ncFSGS cases (\( P = 0.2 \)). Recipients with cFSGS had higher urine protein excretion (11.9 ± 6.7 vs 7.2 ± 9.5 g/24 h, \( P = 0.04 \)) and serum creatinine concentration (4.2 ± 2.6 vs 1.9 ± 0.6 mg/dl, \( P = 0.0001 \)) at the time of biopsy diagnosis. Plasmapheresis therapy was employed in 2 of 10 cFSGS cases and 7 of 19 ncFSGS cases with documented therapeutic response in 0 of 2 and 3 of 7 in ncFSGS, respectively. Of these, neither patient from the cFSGS group and four of eight in ncFSGS group were treated for recurrent disease. During clinical follow-up, graft loss occurred within 3 years in all patients with cFSGS compared with 40% of ncFSGS cases [followed for a mean of 2.5 ± years (\( P = 0.018 \) by Kaplan–Meier analysis, Figure 1].

**Histopathology and in situ hybridization for potential viral pathogens**

Representative photomicrographs of glomerular abnormalities on diagnostic biopsies from cases of post-transplant cFSGS and ncFSGS are shown in Figure 2 (panels A and B). Among the cFSGS biopsies, a mean of 10.7 ± 4.9 glomeruli were present of which 4.9 ± 4.1 demonstrated collapsing features and 2.3 ± 1.4 demonstrated global sclerosis. Among the ncFSGS biopsies, a mean of 12.1 ± 4 glomeruli were present of which 4.1 ± 2.5 demonstrated focal sclerosis and 2.1 ± 1.5 demonstrated global sclerosis. In order to compare the degree of acute and chronic injury at the time of the diagnosis of cFSGS and ncFSGS, all biopsies were scored using Banff ‘97 criteria. The total combined acute and chronic scores as well as combined scores for acute tubulointerstitial, chronic tubulointerstitial and chronic vascular abnormalities were compared for the two groups (Figure 3). As shown,
the mean values for combined total acute and acute tubulointerstitial scores were generally low and comparable for diagnostic cFSGS and ncFSGS biopsies. In contrast, total chronicity scores (excluding glomerular scores) were significantly higher for cFSGS (5.1 ± 3.1 vs 2.2 ± 1.8, P = 0.01). When mean chronic vascular (cv + ah) and chronic tubulointerstitial (ci + ct) scores were compared separately, only the vascular scores were significantly higher among cFSGS biopsies. When arteriolar hyalinosis was analysed separately (as a potential indicator of calcineurin inhibitor (CNI) nephrotoxicity), 3 of 10 cFSGS biopsies had evidence of abnormal arteriolar hyalinosis (ah ≥ 1) compared with 1 of 19 ncFSGS biopsies (P = 0.08 for cFSGS vs ncFSGS). Of the four total cases with abnormal arteriolar hyalinosis on the diagnostic biopsy, three were managed with ciclosporin and one with tacrolimus. The diagnostic biopsies for these cases were carried out 3, 7, 9 (cFSGS cases) and 4 years (ncFSGS case) post-KTx. In no case was isometric vacuolization of tubular epithelial cells or clinical features of acute CNI toxicity present. ISH for pvB19, SV40 and BKV was carried out using established protocols and appropriate positive controls (examples of positive controls shown in Figure 2, panels C and D). No positive staining suggestive of intracellular viral DNA was noted in any allograft biopsy section, essentially ruling out intragraft replication of these viruses among cases of cFSGS and ncFSGS.

Discussion

Collapsing FSGS is a distinct variant of FSGS that may occur in HIV-infected individuals or as an idiopathic form. Irrespective of the aetiology, the clinical course of cFSGS is remarkably uniform and most cases rapidly progress to ESRD [13]. To date, cFSGS has been infrequently reported in the post-transplant setting [3,4,6,14–17] and has only been directly compared with post-KTx ncFSGS in one case series [4], in which five cases each of cFSGS and ncFSGS were studied. The potential role of pvB19 and polyomaviruses in the causation of post-KTx cFSGS has also not been studied in detail although immunosuppressive anti-rejection therapy clearly constitutes a risk factor for infection or reactivation of these viruses [7,18]. The current study represents, therefore, the most comprehensive analysis to date of renal allografts complicated by the development of FSGS with collapsing features. The findings confirm that, similar to the outcome in the non-transplant setting, post-KTx cFSGS consistently results in rapid loss of renal function. In addition, we demonstrate that DNA sequences for pvB19, SV40 and BK viruses were not detectable by validated ISH assays in any case of post-KTx cFSGS or ncFSGS.

Primary FSGS is a relatively common cause of ESRD leading to renal transplantation among children (11.6%) and adults (2–3%), and has been consistently associated with 20–30% post-transplant recurrence rate [19–21]. Existing reports indicate that the cFSGS is uncommonly diagnosed in the post-KTx setting and has been more often identified as a de novo process rather than a recurrent disease [4,14]. Of a series of seven cases reported by Stokes et al. [3], only one carried a pre-transplant diagnosis of cFSGS. This trend is borne out in the current series in which only 2 of 10 cases of cFSGS were considered to represent the recurrence of a primary renal disease. Regarding pre-transplant risk factors for cFSGS in renal allograft recipients, we observed no clear differences in recipient demographic and immunological profiles of the 10 cases identified at our centre compared with ncFSGS cases. Similarly, Meehan et al. [4] observed no predictive pre-transplant demographic or clinical
features in a series of five cases of de novo post-KTx cFSGS occurring in deceased donor allografts. It is of interest that 70% of the cases identified at our institution also occurred in deceased donor grafts—a frequency that was higher than that observed for non-collapsing cases (32%) and considerably higher than our overall frequency of deceased donor kidney transplantation in the time period during which the cases accrued (20%). Of these seven cases of post-KTx cFSGS in deceased donor grafts, all represented apparent de novo disease. While this observation raises the possibility that deceased donor grafts may have increased vulnerability to the development of de novo glomerular collapsing changes, more extensive reporting of this histological finding on renal allograft biopsies will be necessary for confirmation of such an association.

The role of post-transplant factors such as immunosuppressive medication, immunological injury, microvascular disease and infection in the pathogenesis of cFSGS is also not well known. In the report of Meehan et al. [4], the frequency of post-transplant complications, including acute rejection and DGF was not higher than that of other transplant recipients. In the current series, both DGF and acute cellular or humoral rejection occurred commonly in allografts subsequently diagnosed with cFSGS (40 and 70%, respectively) but were no less frequent among ncFSGS cases. Ciclosporin-based immunosuppression was more frequently employed among graft recipients with cFSGS compared with those with ncFSGS (50 vs 10.5%, \(P=0.03\)) while sirolimus-based immunosuppression was more common among ncFSGS cases (10 vs 32%, \(P=0.17\)). A possible role for CNI nephrotoxicity in the pathogenesis of de novo post-transplant FSGS has been raised by Cosio et al. [19] and Nankivell et al. [20] in large studies of glomerular pathology among KTx recipients. Both of these studies demonstrated a correlation between arteriolar hyalinosis and FSGS in the context of biopsy-proven chronic allograft nephropathy (CAN) presenting late post-transplantation. It is of note, therefore, that four of the overall cohort of post-KTx FSGS cases reported here had concomitant arteriolar hyalinosis, were managed by CNI-based immunosuppression and were diagnosed between 3 and 9 years post transplantation. Although not statistically significant, three of four cases occurred among the cFSGS group raising the possibility of a contribution of CNI nephrotoxicity to the pathogenesis of this lesion. It should be emphasized, however, that the overall rarity of cFSGS among patients transplanted during the same time period [10 cases among a total of 1875 KTx (0.5%)] precludes a definitive analysis of whether the use of ciclosporin specifically or CNI therapy in general is associated with an increased risk of developing this lesion. Thus, information regarding anti-rejection therapy on a larger cohort of affected patients from multiple transplant centres would be required to support the conclusion that individual immunosuppressive agents or combinations contribute to or protect against the development of cFSGS.

Chronic histological abnormalities including interstitial fibrosis, tubular atrophy, arterial intimal hyperplasia and arteriolar hyalinosis are common accompaniments of glomerular diseases of native kidneys and their severity typically correlates with renal function and with functional prognosis. In the transplanted kidney, such chronic histological abnormalities frequently occur in the absence of a primary lesion and, under the umbrella term of ‘chronic allograft nephropathy’ (CAN), may be considered to represent the final common pathway of multiple immune and non-immune-mediated injuries to which the allogeneic organ may be susceptible. In this context, it is noteworthy that previous case series reported evidence of CAN in the majority of post-KTx cFSGS biopsies [3]. By applying the Banff ‘97 scoring system for semi-quantitatively estimating the severity of different elements of CAN to the diagnostic biopsies from our case series, we observed that chronic injury was present to a substantial degree in both groups but was more severe in cFSGS compared with ncFSGS. Specifically, the combined scores for arterial and arteriolar damage were higher in the presence of a collapsing glomerular lesion. Recently, Nadasdy et al. [15] showed a zonal distribution of glomerular collapse in relation to obliterative vascular changes on allograft nephrectomy specimens suggesting a role for vascular injury to the causation of cFSGS [15]. Taken together, these observations raise the possibility that pre-existing (due to donor disease) or concomitantly developing microvascular diseases contribute to the histological and clinical profiles that distinguish collapsing and non-collapsing variants of post-KTx FSGS.

The well-recognized association between HIV infection and cFSGS raises the possibility that intrarenal infection by other viral pathogens may also contribute to the development of this lesion in native or transplanted kidneys. A recent report of cFSGS in a patient with post-transplant pvB19-related red cell aplasia and of successful re-transplantation following eradication of this virus, suggested a link between pvB19 and cFSGS [7]. Several additional studies, which have demonstrated the presence of pvB19 or SV40 DNA sequences in renal biopsies of FSGS patients, lend further credence to the hypothesis that these, or other viral pathogens, play a role in the pathogenesis of cFSGS [5,6,9]. In contrast, we found that viral DNA sequences for pvB19, SV40 and BKV were not present in the diagnostic renal biopsies of a combined total of 29 cases of cFSGS or ncFSGS. Though the method of identification (ISH) used in our study can be considered less sensitive than PCR, the negative findings in all the biopsies tested strongly argues against an important role for these viruses in mediating post-KTx FSGS.

Reported experience in the treatment of post-KTx cFSGS is very limited, but the role of plasmapheresis in ameliorating proteinuria is of specific interest. Multiple case series’ document the use of plasmapheresis in the
setting of recurrent FSGS, typically without direct reference to histological subtypes, and no literature is available comparing the response rates of cFSGS and nCFSGS with plasmapheresis. To date, no randomized controlled clinical studies have been carried out. Results from the available literature suggest that the effect of plasmapheresis to decrease proteinuria is variable and, at best, 50% of the patients may respond to the therapy if started early following the onset of recurrence [21–23]. The response to plasmapheresis in our study was comparable with this existing literature for nCFSGS with three of seven patients achieving partial or complete remission of proteinuria. In contrast, neither of the two patients with cFSGS who received plasmapheresis responded. In fact, both experienced marked worsening of renal function shortly after the initiation of the therapy and subsequently their disease progressed rapidly to ESRD. Although the presence of permeability factor-like activity has been reported in the serum of patients with cFSGS of native kidneys [26], reports to date have not distinguished between collapsing and non-collapsing variants when describing the results of plasmapheresis/immunoadsorption for recurrent FSGS. Thus, it remains to be determined whether there is truly a differential therapeutic response. If so, this may simply exist on the basis of more severe glomerular injury among cFSGS cases (as evidenced by higher serum creatinine concentration and urine protein excretion) but could also represent a true pathophysiological difference between the two processes.

It is important to acknowledge that the current study, while incorporating a larger series than has been published to date, is limited by relatively low case numbers. Thus, important aetiological associations, prognostic indices and therapeutic responses for cFSGS and nCFSGS in the post-transplant setting may not have been detected. Nonetheless, we believe that the characteristics of these patient groups identify post-KTx cFSGS as a distinct entity associated with more severe chronic vascular changes on biopsy, worse proteinuria and renal insufficiency, and higher rate of graft loss compared with nCFSGS. Intragraft infection with pvB10, SV40 or BKV is unlikely to mediate either disease. Larger, prospective studies will be necessary to compare the relative effectiveness of plasma exchange and other therapies in post-KTx nCFSGS and cFSGS.

Acknowledgements. The authors wish to acknowledge the expert advice and direction of Dr Ricardo V. Lloyd in the performance of in situ hybridization for this study.

Conflict of interest statement. None declared.

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Received for publication: 14.1.06
Accepted in revised form: 27.3.06