Original Research Article

Collapsing glomerulopathy in renal allograft biopsies: A study of five cases

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Abstract

Collapsing glomerulopathy (CG) is considered to be a distinct clinic pathologic pattern of proliferative podocyte injury. The clinical significance of CG in renal allograft biopsies is not yet clear due to the scant data on the occurrence of CG in renal transplant recipients. We identified nine cases of CG in allograft biopsies over a period of 1 year. Detailed clinical information, including follow-up data, was collected and histopathological analysis performed. All the five patients were males with a mean age at diagnosis of 37.8 years. The median post transplantation duration at diagnosis was 36 (range 12–84) months. All the patients presented with severe proteinuria and graft dysfunction. Histological analysis showed a median number of 7 glomeruli. The collapse of the glomerular tuft with visceral epithelial cell hyperplasia involved median of 2 glomeruli (range 1–4). At the last follow-up (mean duration 6 months), two patients had graft failure (return to dialysis) while three had functioning grafts. This series emphasizes the importance of this rare glomerular pathology as an important cause of graft dysfunction that may lead to allograft failure.

Key Word: Collapsing glomerulopathy, histopathology, outcome, renal allograft.

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INTRODUCTION

Collapsing glomerulopathy (CG) was recognized in 1978 as a variant of focal and segmental glomerulosclerosis (FSGS), especially associated with HIV infection[1].Later reports showed the occurrence of CG in HIV-negative patients as well and this entity was called "collapsing FSGS[2]." Recent studies suggest that CG is a distinct clinicopathologic entity, not related to FSGS due to the differences in the clinical presentation, histologic appearance, and outcome[3]. The occurrence of CG in renal allografts has been reported as case reports and small studies[4-7].In the previous studies, patients had presented with graft dysfunction and proteinuria, varying from few days in recurrent cases to many years after transplantation in *de novo* CG. The long-term outcome of the previously reported patients has been unfavorable with most of the patients returning to dialysis [7,8]. However, the appropriate therapeutic management of this rare pathology is still unclear. This series presents the clinical and pathologic features of nine renal transplant recipients with CG in allograft biopsies over a period of 1 year.

MATERIALS AND METHODS

All renal allograft biopsies received by our department between 2018 and 2019 were reviewed. CG was diagnosed on the basis of diffuse or focal, segmental or global glomerular capillary collapse with hyperplasia/ hypertrophy of overlying visceral epithelial cells (podocytes). During the study period, five such biopsies were identified. Clinical data were obtained from a review of the patients' medical records. The details recorded were age, sex, duration of transplant, pretransplant biopsy diagnosis, and immunosuppressive regimen along with severity of proteinuria, and allograft dysfunction. Serological investigations for viral infections (HIV, hepatitis B [HBV], parvovirus) were also recorded. Prior rejection episodes and drug toxicity (especially

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calcineurin inhibitors [CNIs]) were documented. Renal biopsy tissues were processed for light microscopy and immunofluorescence microscopy by standard techniques. For light microscopy, sections were stained with hematoxylin and eosin, periodic acid Schiff, and silver methenamine stains. Interstitial fibrosis and tubular atrophy were graded semi-quantitatively on a scale of 0 to 3 (absent, up to 25%, 26–50%, >50%, respectively). In addition, cellular rejection was identified and graded according to the Banff 2017 update [10]. CNI toxicity was identified by the presence of peripheral nodular arteriolar hyalinosis and/or a "striped" pattern of interstitial fibrosis and tubular atrophy.

RESULTS

A total of 65 renal allograft biopsies were performed during the study period (2018–2019). Of these, five showed features of CG, constituting 7.5% of all allograft biopsies. All these five patients had undergone renal allograft biopsy for the evaluation of graft dysfunction and proteinuria. All the five patients were males with an age ranging from 24 to 55 years (average 37.4 years). These patients were diagnosed as CG in the allograft biopsy at a median of 36 months after transplantation (range 12–84 months). All the patients received allografts from living donors (mother 3, sister 1, and wife 1). The native kidney disease was unknown in three of these patients, for the other two it was diabetic nephropathy. Of the five patients, two presented with pedal edema while the other three underwent biopsy for asymptomatic graft dysfunction (median serum creatinine 3.4 mg/dl; range 1.3–5.5 mg/dl). All the patients had proteinuria with 24-h urinary protein excretion ranging between 2.5 and 5.8 g/day. All the five patients were receiving steroid-based triple drug immunosuppression (tacrolimus in all). The serum CNI trough levels were within expected ranges in all the patients at the time of biopsy. The salient clinical features are summarized in Table 1.None of the patients had a prior episode of acute rejection. All the patients were negative for HIV, HBV and parvovirus by serology.

	1	2	3	4	5
Age/ sex	24/M	26/M	39/M	45/M	55/M
Time of biopsy					
Indication for biopsy	CGD	CGD	CGD	PEDAL EDEMA	PEDAL EDEMA
Serum creatinine	3.5	1.3	2.0	4.8	5.6
Urine protein	3.4	1.6	2.2	5.4	6.0
Hypertension	+	+	+	+	+
Follow-up(months)	12	2	6	10	12
outcome	4.2	2.0	1.5	Graft failed	Graft failed

The pathologic findings of our five cases are listed in Table 2. The number of glomeruli was 7.

	1	2	3	4	5
No. of glomeruli	7	7	6	8	10
Global sclerosis	5	3	0	5	6
Segmental collapse	2	1	1	3	3
Other injury	-	-	-	-	-
IFTA	20-30%	20-30%	10%	40%	60-70%
TCMR	-	ACR 1A	-	-	-

All the biopsies had one or more (14 –37.5%) glomeruli showing a segmental collapse of the tuft with swollen hypercellular podocytes overlying the collapsed tuft. The podocytes in these foci showed nuclear enlargement, prominent nucleoli, and PAS positive intracytoplasmic droplets [Figure 1]. Diffuse interstitial fibrosis, involving more than 50% of the cortical parenchyma and accompanying tubular atrophy, was seen in one case (20%) while the other four biopsies showed mild to moderate degree of tubulointerstitial changes. None of the cases showed viral cytopathic effects or histological features suggestive of CNI toxicity (a striped pattern of tubular atrophy/interstitial fibrosis with/without peripheral nodular arteriolar hyalinosis). Immunofluorescence could be performed in only four cases, of which two showed diffuse granular capillary wall staining for IgA (3+) consistent with IgA nephropathy with CG. Other two biopsies showed no significant immunofluorescence findings.

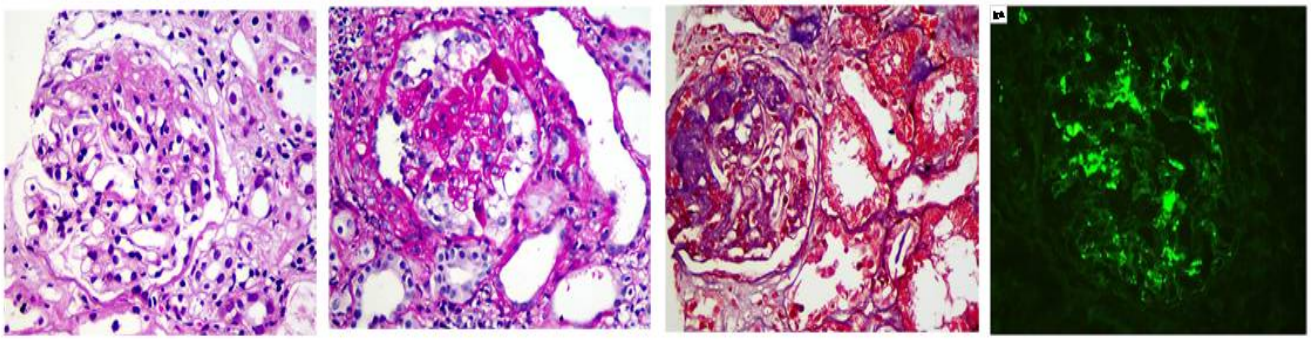

Figure 1: Photomicrographs from cases of collapsing glomerulopathy showing a glomerulus with the collapse of the tuft and hyperplasia of overlying visceral epithelial cells (a, H and E ×100). Higher magnification shows segmental involvement of the glomerular tuft (b, H and E ×400). The visceral epithelial cells demonstrate prominent intracytoplasmic droplets (c, H and E ×400). The silver methenamine stain highlights the segmental tuft collapse associated with hyperplasia of visceral epithelial cells (d, ×200). Immunofluorescence microscopy shows IgA dominant pattern. microscopy shows IgA dominant pattern.

DISCUSSION

CG was initially described as "malignant FSGS" in 1978 due to the clinical presentation of rapidly progressive nephrotic syndrome[1]. In the era of HIV pandemic, CG came to be identified as "HIV-associated nephropathy." In 1986, Weiss *et al.* described a similar renal lesion in HIV-negative patients and the term "collapsing glomerulopathy" was used to indicate this entity[11]. The concept that CG was related to FSGS was introduced by Detweiler *et al.* and the entity was known as "collapsing FSGS."[2, 12] Many authors now prefer to use "collapsing glomerulopathy" on the basis of histologic, pathogenetic, and clinical differences between CG and FSGS[3]. Both recurrent and *de novo* CG with features similar to those in native kidney have been scantily described in renal allograft biopsies. Only a few reports and small studies were found in the available literature.[4-9,13] One of the studies reported a frequency of 3.2% CG in allografts[7], comparable to 7.5% noted in the present study. In the previous reports, recurrent CG in renal allografts have presented with nephrotic syndrome with/ without graft dysfunction soon after transplantation while *de novo* CG has been diagnosed as late as 74 months posttransplantation[5, 8, 13]. The median duration of transplant in the present study was 36 months, with one patient diagnosed with CG 84 months after transplantation. All the patients had graft dysfunction and two had come with pedal edema. Due to the relatively recent recognition of this entity, there is no consensus on the appropriate therapeutic regimen for CG. This is especially true for CG occurring in renal allografts, either recurrent or *de novo*. Most of the reported cases had progressive worsening of renal functions with return to dialysis at a variable period after the biopsy diagnosis of CG [6-8]. In the study by Meehan *et al.*, all five patients developed graft failure within 24 months after the diagnosis of CG[7]. Another study of seven patients reported return to dialysis in five patients within 3–4 months after the diagnosis. One of these five patients had CG in the native kidney[8]. In the present study, two patients had graft failure while the other three patients had functioning grafts. Accurate recognition of this distinct clinic pathologic entity and its differentiation from FSGS is essential for the appropriate prognostication of an individual patient. Unlike the previously reported cases, the outcome in our patients was not uniformly unfavorable. Of the five patients in whom follow-up data were available, two had graft failure. Although it is difficult to categorically state the reason for this, the detection of CG early in the course of disease when renal functions were not compromised severely might have contributed to this favorable outcome. In conclusion, CG must be recognized as a cause of graft dysfunction, especially in patients with detectable proteinuria. All such patients should be investigated for known associations like viral infections, drug toxicities, and vascular injury. Since the outcome of allografts with collapsing glomerulopathy may not be favorable, a close follow-up is mandatory. More such studies of collapsing glomerulopathy in renal allografts are required to delineate the prognostic significance of this entity.

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