The Interesting Case

Collapsing glomerulopathy—recurrence in a renal allograft

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Introduction

Focal segmental glomerulosclerosis (FSGS) is a common cause of idiopathic nephrotic syndrome, accounting for 10–15% of cases in children and a higher proportion in adults. Several studies have documented an increasing incidence of FSGS in renal-biopsy specimens over the past two to three decades [1–3]. Concurrent with this increasing incidence, a new clinicopathological variant of FSGS was first described by Weiss et al. [4] in 1986 characterized by severe nephrotic syndrome, rapid progression to end-stage renal disease over months, and features of visceral epithelial cell injury and glomerular ‘collapse’. The authors proposed that ‘collapsing glomerulopathy’ is a clinicopathological entity distinct from other forms of idiopathic FSGS, a view supported subsequently by Deitweiler et al. and Valeri et al. [3,5]. Here we present a case of ‘collapsing glomerulopathy’ that recurred after renal transplantation. The clinical presentation, histological features, pathophysiology and treatment of this emerging glomerulopathy are discussed.

Case report

A 62-year-old woman presented in August 1992 with nephrotic syndrome and renal failure (serum creatinine 326 µmol/l). A renal biopsy at that time revealed diffuse epithelial cell injury with segmental glomerular capillary collapse and active interstitial inflammation. Over the ensuing 8 months her nephrotic syndrome did not remit on prednisolone or cyclophosphamide. A second biopsy showed features characteristic of collapsing glomerulopathy (see Figure 1). The patient developed systemic hypertension, progressive anasarca, and renal insufficiency, and was initiated on maintenance haemodialysis in April 1993.

In November 1993 the patient received a renal allograft from her son which functioned well for 3 days. Acute renal failure developed at day 4 eventually requiring haemodialysis. An allograft biopsy showed tubulointerstitial and vascular changes of acute rejection. She received intravenous methylprednisolone therapy followed by a 7-day course of OKT3 without improvement in allograft function. A repeat biopsy on day 11 revealed mild focal interstitial inflammation and no signs of vascular rejection; the glomeruli in this biopsy were unremarkable. Her hospital course was complicated by an E. coli urinary-tract infection which responded to ciprofloxacin. Atrial fibrillation on day 6 was treated with digoxin. Anuria supervened on day 10. Herpetic lesions of the oral mucosa on day 17 were treated with oral acyclovir. A diarrhoeal episode on day 19 was treated with vancomycin. Leukopenia developed on day 26, necessitating a reduction in the dose of azathioprine. A repeat biopsy on day 19 did not show signs of rejection or glomerulopathy. On day 20, an antegrade allograft nephrostogram was notable for the absence of anatomical strictures or signs of hydrenephrosis. The patient was discharged 4 weeks after transplantation on conventional triple immunosuppressive therapy and haemodialysis.

The patient’s urine output increased over the ensuing 2 weeks, her serum creatinine fell and haemodialysis was discontinued. At week 26 post-transplantation, when her serum creatinine was 236 µmol/l, she was noted to have heavy proteinuria (14 g/24 h) and overt nephrotic syndrome. A renal biopsy showed characteristic findings of collapsing glomerulopathy.

Discussion

Collapsing glomerulopathy accounted for up to 25% of cases of idiopathic FSGS in a recent large renal...
biopsy series [3] and underscores the critical role of the glomerular visceral epithelial cell in the maintenance of glomerular architecture and regulation of urine protein excretion. The term ‘collapsing glomerulopathy’ was coined to highlight the prominent collapse of glomerular capillary loops with retraction and wrinkling of the glomerular capillary membrane (Figure 1).

Glomerular collapse can be global or focal; the former being the more usual. The number of involved glomeruli varies among studies, but averages >50% of all glomeruli. Notably capillary loop collapse is not accompanied by prominent mesangial expansion, hyalinosis, or adhesion to Bowmans capsule, distinguishing collapsing glomerulopathy from other forms of idiopathic FSGS. There is marked visceral epithelial cell prominence with associated intracytoplasmic hyaline inclusion droplets (Figure 1). Indeed, epithelial cell prominence can be so marked as to mimic crescent formation. Close examination, however, reveals that the increased epithelial cell mass is due to cellular swelling rather than cellular proliferation. Collapsing glomerulopathy is also characterized by marked tubulointerstitial disease out of proportion to the inflammation normally seen in idiopathic FSGS (Figure 1). Tubular necrosis, dilatation, atrophy, degeneration, and regeneration are common findings, and typically are accompanied by severe interstitial oedema, inflammation, and fibrosis. The findings on immunofluorescence microscopy are non-specific and include variable mesangial deposition of IgM, C3 and C1. Hyaline resorption droplets may also stain strongly positive for albumin (Figure 1), and also for immunoglobulin and complement.

Electron-microscopy reveals prominent effacement of epithelial cell foot process. Other epithelial cell changes on ultrastructural analysis include an increase in cytoplasmic volume and inclusion bodies, and villous transformation. The capillary basement membrane diameter is frequently wrinkled, but appears otherwise normal. Collapsing glomerulopathy shares many histological findings with human-immunodeficiency-associated nephropathy (HIVAN); however, the characteristic intraendothelial tubuloreticular inclusion of HIVAN are nearly always absent.

Collapsing glomerulopathy usually presents clinically with heavy proteinuria or overt nephrotic syndrome, and abnormal renal function that progresses rapidly to end-stage renal failure. The latter renal presentation is preceded 3–9 months beforehand by a prodrome of non-specific symptoms which include oedema, malaise, anorexia, and dyspnoea in the majority of patients. Most patients are hypertensive at presentation. There is a marked black racial predominance in collapsing glomerulopathy, as in HIVAN. In

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Fig. 1. Typical histological features of collapsing glomerulopathy. (a) This low-power light-micrograph shows characteristic glomerular, tubular and interstitial changes seen in collapsing glomerulopathy. The glomerulus reveals global collapse of capillaries; prominent tubular changes include extensive cast formation, dilatation of tubules (‘microcysts’), and degenerative changes of the tubular epithelium. There is also focal interstitial infiltration by mononuclear inflammatory cells (left) (PAS). (b) Details of the glomerular changes. There is prominence of the epithelium, which shows widespread vacuolization. Protein resorption droplets are often visible (not shown). The underlying capillary network is collapsed; most of the open spaces represent epithelial cell vacuoles (PAS). (c) Immunofluorescence-microscopy shows no immune deposits but prominent protein resorption droplets in the epithelial cells (direct immunofluorescence-microscopy, anti-albumin).
the first report by Weiss et al. [4], all six patients were African-American, one of whom subsequently proved to be infected with HIV and, in fact, have been an unrecognized case of HIVAN. In the studies by Dietweiler et al. and Valeri et al. 81% and 61% of patients respectively were of African-American ancestry [3,5]. The male-to-female ratio also mimics HIVAN with a significant male predominance. By comparison with other variants of FSGS, patients with collapsing glomerulopathy have significantly heavier proteinuria at presentation and a trend towards a lower serum albumin [4]. In Dietweiler’s group of sixteen patients, the median protein loss was $13.2 \pm 7.7 \text{ g/24 h}$ [5]. Patients with the collapsing variant also tend to have a higher initial serum creatinine and more rapid progression to ESRD. Valeri et al. estimated the median time from biopsy to ESRD to be 13 months in collapsing glomerulopathy as opposed to over 60 months in other forms of idiopathic FSGS [3].

The pathogenesis of collapsing glomerulopathy is incompletely understood. The clinical and pathological features point to the visceral epithelial cell as the major target of injury. The mediators of visceral cell injury have yet to be established. The non-specific nature of immunoglobulin deposition on immunofluorescence microscopy argues against antibody-mediated glomerular injury. Some though not all patients report a prodrome suggestive of a viral illness, typically with fever, malaise, and anorexia. The similar morphological features of collapsing glomerulopathy and HIVAN point to a viral etiology. It is possible that a virus directly infects the visceral epithelial cell and perturbs its function, or induces injury indirectly by stimulating systemic release of tubulotoxic cytokines or other inflammatory mediators. It has been demonstrated that mice transgenic for viral genes, including HIV, develop glomerular lesions remarkably similar to those seen in HIVAN, and HIV RNA has been demonstrated in glomerular tissue in HIV-positive patients [8,9]. It remains speculative, however, as to whether or not retroviral genomic incorporation into human renal tissue contributes to the development of either HIVAN or collapsing glomerulopathy. HIV itself is not the aetiological agent in collapsing glomerulopathy; however, a similar pathological response to different exogenous stimuli remains a possibility.

Given its relatively recent description as a distinct clinicopathological entity, no prospective data exists on the treatment of collapsing glomerulopathy. Retrospective observations suggest that conventional immunosuppression with steroids and cyclophosphamide is ineffective as a means of reducing proteinuria or slowing progression to ESRD [3–5]. There is some suggestion from the study by Valeri et al. that cyclosporin may be of benefit. Of three patients treated with cyclosporin, one had a partial response and one a complete remission. Spontaneous remission was also noted in this study, so treatment ‘responses’ must be viewed with caution [3].

In our case, collapsing glomerulopathy recurred in a renal allograft. Interestingly, collapsing glomerulopathy has also been described de novo in renal allografts [10]. The incidence of graft recurrence in idiopathic FSGS is between 20 and 30% [11,12]. There is limited experience of transplantation in patients with collapsing glomerulopathy. Four patients reported by Weiss et al. and seven patients reported by Valeri et al. underwent renal transplantation without evidence of recurrent disease at follow-up, suggesting a low incidence of this complication.

‘Collapsing glomerulopathy’ adds to the expanding list of clinicopathological entities that can present with nephrotic-range proteinuria and acute or subacute renal failure (Table 1). The constellation of clinical and pathological features that typify collapsing glomerulopathy highlight the capacity of visceral epithelial cell injury alone to trigger azotaemia and nephrotic syndrome. Less dramatic injury to the visceral epithelial cell can also be associated with azotaemia when accompanied by proximal tubule injury [13] or allergic interstitial nephritis [14]. The further delineation of the aetiological agents and inflammatory mediators that trigger epithelial cell injury under these circumstances should shed light on the complex function of glomerular visceral epithelium, and suggest novel approaches to therapy.

### References


### Table 1. Major causes of acute renal failure in association with nephrotic range proteinuria

- Compensatory/iatrogenic
- Prerenal failure due to overzealous diuretic use and/or hypoalbuminaemia
- Manifestation of glomerulopathy
- Collapsing glomerulopathy
- Minimal-change glomerulopathy with acute tubular necrosis
- Minimal-change glomerulopathy with allergic interstitial nephritis
- Miscellaneous
  - Myeloma cast nephropathy
  - Nephrotic syndrome complicated by renal vein thrombosis


