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Editorial Comment

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Viruses and collapsing glomerulopathy: a brief critical review

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Abstract

Background. Collapsing glomerulopathy may occur in an idiopathic (primary) form and in association with a wide spectrum of infectious and inflammatory conditions and medications. The association of collapsing glomerulopathy with human immunodeficiency virus (HIV)-1 infection is well established; less certain is the association with other viral infections.

Methods. We searched PubMed for articles in all languages that addressed glomerulopathies associated with parvovirus B19, cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis C virus (HCV) and simian virus 40 (SV40).

Results. Case reports and small-case series link infection with these common viruses and glomerular injury. The evidence for a pathogenic role is generally stronger for glomerulonephritis than for collapsing glomerulopathy.

Conclusions. The evidence linking collapsing glomerulopathy with CMV is relatively strong but not yet conclusive, while the evidence for a pathogenic role for EBV and parvovirus B19 is weaker.

Keywords: collapsing focal segmental glomerulosclerosis; cytomegalovirus; Epstein-Barr virus; parvovirus B19; podocyte

Collapsing glomerulopathy may be considered either a variant of focal segmental glomerulosclerosis (FSGS) [1] or a distinct pathologic entity [2], but there is general agreement on the key histologic features. The term 'collapsing glomerulopathy' was first described by Weiss *et al*. to describe a distinct entity with progressive renal failure and pathological features characterized by segmental or global glomerular capillary collapse and visceral epithelial cells swelling and hyperplasia with hyaline droplets and extensive tubulointerstitial inflammation [3]. Subsequent studies from Detwiler *et al*. and Valeri *et al*., including subjects with and without HIV infection, reported a similar pathologic phenotype. Compared with patients with classic FSGS, patients with collapsing glomerulopathy were more likely to be of African descent and had higher serum creatinine, more proteinuria at the time of kidney biopsy and worse renal survival [4, 5]. Compared with classic FSGS, collapsing glomerulopathy less likely causes sclerosis and hyalinosis of the capillary tuft and capsular adhesions. The collapsing variant of FSGS is defined by the Columbia classification as the presence of segmental capillary tuft collapse (wrinkling and folding) in at least one glomerulus. It is characterized by global or segmental collapse of the glomerular capillary walls associated with wrinkling of the glomerular basement membrane. There is marked hypertrophy and hyperplasia of the visceral epithelial cells sometimes forming pseudocrescents. These are differentiated from true crescents by the lack of intercellular matrix or attachment to the Bowman's capsule [6].

The mechanism that leads to the altered phenotype of the visceral epithelial cells in collapsing glomerulopathy is not well understood. Barisoni *et al*. noted that these cells lacked certain podocyte differentiation markers, including Wilms tumor 1, synaptopodin, podocalyxin, PTPRO/GLEPP1 and C3B receptor [7]. Further, podocytes are normally terminally differentiated, non-dividing cells. In collapsing glomerulopathy, the visceral epithelial cells re-enter the cell cycle, as evidenced by KI-67 expression [7] and in a genetic mouse model of collapsing glomerulopathy, expression of cyclin D1 and reduced expression of cyclin-dependent kinase inhibitors such as p27 and p57 [8] . Evidence has been put forward implicating increased levels of human telomerase reverse transcriptase and Wnt signaling in the altered podocyte phenotype [9]. These features suggested a process of podocyte dysregulation, distinct from either injury or dedifferentiation. This morphological and gene–protein expression profile is similar in HIV-associated and idiopathic collapsing glomerulopathy. An important advance has been the recognition that in collapsing glomerulopathy, visceral epithelial cells bear markers of the parietal epithelium [10] and may represent replenishment from a glomerular stem cell pool that is present within the parietal epithelium [11, 12]. The molecular mechanisms that lead to the postulated excessive and dysregulated stem cell replacement remain to be defined. Relevant to the current topic, a better understanding of the role that viral infection and viral gene products play in altered glomerular cell biology may help define relevant physiologic pathways and may suggest possible therapeutic targets for

collapsing glomerulopathy for diverse forms of collapsing glomerulopathy.

Collapsing glomerulopathy has been associated with several conditions including infections due to viruses, *Mycobacterium tuberculosis*, filariasis (Loa loa), leishmaniasis, *Campylobacter* enteritis; autoimmune diseases, including lupus and adult Still's disease; malignancies, including natural killer cell leukemia and hemophagocytic syndrome; genetic mutations, including certain mitochondrial disorders; medications, including interferon alpha, beta and gamma, and pamidronate; and following kidney transplantation. A number of excellent recent reviews are available [13, 14]. For many associations, the number of cases is few, particularly considering the frequency of the co-occurring disease, which raises the possibility of a chance occurrence.

Our goal will be to review the strength of the evidence linking particular viral infections with collapsing glomerulopathy and to some extent, with glomerular disease in general (Table 1). Our focus will be on three DNA viruses: Epstein-Barr virus (human herpesvirus-4), cytomegalovirus (CMV, human herpesvirus-5) and parvovirus B19. Individuals are most commonly infected with these viruses in childhood, although in the industrialized world primary infection may be delayed until adolescence or adulthood. All three viruses may establish latent infections in particular tissues.

The association between HIV-1 infection and collapsing glomerulopathy has been well established and will not be reviewed further here. When we move beyond HIV infection, there are reports that suggest that other viral infections are associated with collapsing glomerulopathy. What are the criteria that might be applied to determine causation in these settings, given the practical difficulties in applying Koch's four postulates to many of these clinical problems? The following might be considered as important elements in building a case that a particular virus is the cause of collapsing glomerulopathy.

- *Demonstration of collapsing glomerulopathy occurring in multiple cases involving viral infection.* It is quite possible that viral infection of the glomerulus may cause collapsing glomerulopathy in only a fraction of patients with a particular viral infection. Further, a virus may cause collapsing glomerulopathy in some patients and cause another histologic variant in other patients, or cause minimal pathologic changes. HIV infections provide an example, where individuals with the risk genotype (two *APOL1* risk alleles) most likely manifest either collapsing glomerulopathy [15] or classic FSGS [16] and individuals lacking risk alleles (e.g. persons of European descent) tend not to have these forms of glomerulopathy.

- *Demonstration of clear-cut collapsing glomerulopathy including elements of both glomerular tuft collapse and altered visceral epithelial cell phenotype*. There can be a range of manifestations, from a single glomerulus with a cluster of prominent podocytes coupled with a collapsed glomerular segment to global glomerular collapse with numerous cells in Bowman's space. Thresholds for the diagnosis of collapsing glomerulopathy may differ among pathologists, which can be problematic.

- *Demonstration of viral protein or nucleic acid within glomerular cells, and particularly localization to podocytes*. Evidence for infection should be sought, but it is possible that glomerular injury may be found in the absence of evidence for infection, if collapsing glomerulopathy is due to a bystander effect of virus-driven inflammatory response or due to circulating viral gene products. Further, it may not be possible to use conventional markers of differentiated podocytes such as nephrin, podocin, synaptopodin and protein tyrosine receptor phosphate type O (alternatively known as GLEPP1), as expression of these markers may be lost. In this case, the infected cells are shown to be dysregulated podocytes or stem cells by expression of particular markers or inferred to be these cell types by their characteristic location, e.g. within Bowman's space. Appropriate controls are important, ideally including non-viral forms of collapsing glomerulopathy.

- *Demonstration that viral infection in experimental animals induces some of (or all) the features of collapsing glomerulopathy*, which may be a difficult

Table 1. Renal manifestations of selected viral infections.

	Collapsing glomerulopathy	Other glomerulopathies associated with infection	Tubulointerstitial disease
HIV-1	Established cause	FSGS Mesangial proliferative glomerulonephritis, including IgG predominance, IgA predominance and 'full house' immunoglobulins Thrombotic microangiopathy	Microcystic tubular dilatation is characteristic
Parvovirus B19	Possible cause	Mesangial proliferative glomerulonephritis, leukocyte infiltration, mesangiolysis (some) cases, IgG predominance Mesangial proliferative glomerulonephritis with predominance of IgA (Henoch-Schönlein-like) Thrombotic microangiopathy	Interstitial nephritis
CMV	Probable cause	Mesangial proliferative glomerulonephritis Membranoproliferative glomerulonephritis Diffuse mesangial sclerosis Membranous nephropathy Thrombotic microangiopathy	Interstitial nephritis
EBV	Possible cause	Mesangial proliferative glomerulonephritis Crescentic glomerulonephritis Membranous nephropathy	Interstitial nephritis

Four viruses are plausible causes of collapsing glomerulopathy, and each of these viruses has other renal manifestations.

proposition when the susceptible host range is restricted. Alternatively, it may be possible to demonstrate that viral gene products expressed in transgenic animals induce collapsing glomerulopathy.

Parvovirus B19 was first associated with glomerulonephritis in seven patients with sickle cell disease, in whom acute infection and the consequent aplastic crises were associated with segmental proliferative glomerulonephritis and associated at a later stage with FSGS [17]. Tubulointerstitial changes varied from severe to absent. Subsequent case reports described similar findings in children and adults with primary parvovirus B19 infections, showing either segmental or global endocapillary proliferation, sometimes with mesangiolysis and with immunoglobulin and complement C3 deposition most intense along the glomerular capillary wall and electron dense deposits located in the subendothelial space and the mesangium [18], [19]. In one case, there was predominantly IgA deposition resembling Henoch–Schönlein syndrome [20]. Murer *et al*. described four cases of thrombotic microangiopathy occurring in kidney transplant during acute parvovirus B19 infection [21].

Parvovirus DNA was present in kidney tissue [22–24], although the presence of viral genome in circulating immune cells cannot be excluded as a source of this signal and DNA was localized to glomerular endothelial cells [20] but not to visceral epithelial cells. In some but not all cases studied, parvovirus antigens were localized to glomerular cells that were not further characterized [19, 23], but were entirely absent in six cases [25]. Thus, a major unresolved issue is the localization of parvoviral nucleic acid and protein within kidney tissue from individuals with parvovirus B19 infection; it is unclear whether this is due to methodologic or biologic differences or to inclusion of subjects lacking parvoviral infection or at different stages of glomerular disease evolution [26].

An association between parvovirus B19 and collapsing glomerulopathy was first noted by Moudgil *et al*. in a renal transplant patient [27]. Subsequently, these investigators reported the following rates of PCR detection of parvovirus B19 DNA in archival, paraffin-embedded kidney tissue: collapsing glomerulopathy, 18 of 23 cases (78%); HIV-associated nephropathy, 3 of 19 cases (16%); FSGS, 6 of 22 cases (22%); controls including hematuria, thin basement membrane disease, minimal-change nephropathy and tumor nephrectomy samples, 6 of 27 cases, (22%) [28]. Parvoviral DNA was localized to glomerular parietal cells and visceral epithelial cells using *in situ* hybridization. In a replication study, Tanawattanacharoen *et al*. amplified parvoviral B19 DNA from frozen tissue blocks and found a marginally higher prevalence of parvoviral DNA in collapsing glomerulopathy (9 of 10 cases) and FSGS (8 of 10 cases) but also found viral DNA in membranous nephropathy (6 of 10 cases), minimal-change nephropathy (5 of 10 cases) and tumor nephrectomy (2 of 4 cases) [29]. *In situ* hybridization studies were not able to identify the cellular location of the parvoviral DNA, despite suitable positive control tissue (parvovirus B19 infected placental tissue), suggesting that viral copy number may be low in kidney tissue. Thus, while the results of the two studies differ numerically, the combined dataset suggests that parvoviral DNA is frequently detected in kidney tissue, and the rates are highest in diseases associated with podocyte/visceral epithelial cell dysfunction. These data may indicate that kidney tissue is a location where latent DNA remains long after primary infection with this common childhood viral illness, and that re-emergence may be associated with collapsing glomerulopathy or FSGS in particular. The data, at present, appear to be insufficiently strong to establish a causative role for parvovirus B19 in collapsing glomerulopathy; the data could also be due to glomerular or other cells experiencing reactivation of a latent viral infection as a result of cell injury or dysregulation (podocyte) or differentiation (parietal epithelial stem cell).

The first glomerular diseases associated with CMV infection were in the setting of congenital infection, and included proliferative glomerulonephritis, sometimes with necrotizing features [30], and diffuse mesangial sclerosis [31]. Evidence for a direct role of viral infection included cytomegalic inclusion bodies and/or viral particles within glomerular cells. CMV-associated renal infections have perhaps been most frequently described in the setting of renal transplant. In a recent series from India, Rane *et al*. described 10 cases with involvement of glomeruli (three cases), tubulointerstitium (six cases) or both (one case) [32]. The characteristic viral cytopathic changes were seen in glomerular endothelial cells and podocytes; three patients had thrombotic microangiopathy. Other glomerular disease reports associated with CMV infection have described membranoproliferative glomerulonephritis [33], membranous nephropathy [34] and thrombotic microangiopathy [35]; the links are based on the temporal relationship with infection and in some cases, response to anti-viral therapy.

Collapsing glomerulopathy has been reported in three cases of acute CMV infection, occurring in imumunocompetent individuals. Presne *et al*. described a 16-year-old male with abrupt onset of nephrotic syndrome, renal biopsy showing collapsing glomerulopathy and improvement following therapy with glucocorticoids and ganciclovir [36]. Tomlinson *et al*. described a 60-year-old woman with acute nephrotic syndrome illness and acute CMV infection, with viremia and IgM antibodies [37]. A renal biopsy showed collapsing glomerulopathy and CMV DNA was detected (but not localized) in the renal biopsy by PCR. The patient progressed rapidly to end-stage kidney disease. In this issue of the *Clinical Kidney Journal*, Grover *et al*. described a 34-year-old man who presented with acute CMV infection with viremia and IgM titers, nephrotic range proteinuria and renal failure requiring hemodialysis [38]. A renal biopsy showed findings consistent with collapsing glomerulopathy. CMV DNA was not detected in renal biopsy tissue, although the methods were not described. Therapy with ganciclovir (4 weeks) and glucocorticoids (6 months) was associated with improved renal function, allowing her to stop chronic dialysis. All three individuals were of Caribbean descent, either African or Hispanic ancestry, and thus, possibly carry *APOL1* renal risk alleles that predispose to collapsing glomerulopathy [39]. None of the cases showed characteristic cytomegalic changes in the kidney, specifically not in glomeruli. Nevertheless, taken together, these cases provide substantial evidence that acute CMV infection is a cause of collapsing glomerulopathy and further suggest that therapy with glucocorticoids and anti-viral therapy may be beneficial in stabilizing or reversing glomerular cell injury.

Epstein-Barr virus (EBV) infection has been associated with idiopathic chronic interstitial nephritis, with viral DNA localized to tubular epithelial cells [40]. Viral DNA was similarly localized in the case of an HIV-infected individual with interstitial nephritis [41], but viral DNA

was not found in cases of idiopathic acute interstitial nephritis [42, 43]. Kunimoto *et al*. hypothesized that EBV contributes to IgA nephropathy, but no viral DNA was found in kidney tissue in a case series [44]. A case report described a case of acute EBV infection associated with crescentic glomerulonephritis; while viral protein and nucleic acid localization studies were not performed, but the temporal association suggests that EBV played a role, possibly via immunologic response [45]. Four cases of EBV-associated membranous nephropathy have been reported [46–48]—one case with acute viral syndrome, one case associated with chronic viremia and two cases with malignancy. Recently, Joshi *et al*. reported in the *Clinical Kidney Journal* a case of a young woman who presented with acute EBV infection and collapsing glomerulopathy [49]. *In situ* hybridization studies failed to identify EBV DNA in kidney tissue. To summarize the glomerular diseases reported with EBV infection, it appears that EBV may cause membranous nephropathy (likely via a planted antigen and *in situ* formation of immune complexes), crescentic glomerulonephritis (possibly via immunologic mechanisms) and perhaps collapsing glomerulopathy (via unknown mechanisms), although more cases will be required to strengthen the association.

It is quite possible that other viruses cause idiopathic collapsing glomerulopathy. Hepatitis C virus (HCV) has been associated with collapsing glomerulopathy in four cases, excluding those cases involving co-infection with HIV [50, 51], but viral RNA or protein has not been localized to glomeruli and to date there has been no evidence that HCV plays a pathogenic role. Simian virus 40 (SV40) is a monkey virus present in primary rhesus monkey kidney cells that were used to grow poliovirus in the period 1955–1963; whether SV40 infections occur in human population at present is a subject of considerable controversy [52, 53]. Four groups have investigated a possible role of SV40 in human glomerular disease, including collapsing glomerulopathy and FSGS. Two reports presented evidence against such infections [54, 55] and two reports (including a report by one of the present authors) presented preliminary evidence for such infections [56, 57]. Viral DNA and protein have not been localized to the kidney. It is our present opinion that the evidence for SV40 infections associated with human glomerular disease is weak and that a causal role is unlikely.

In conclusion, the evidence suggesting that several viruses, certainly HIV-1, probably CMV and possibly parvovirus B19 and EBV, have the potential to cause collapsing glomerulopathy. The diagnosis of a viral infection has therapeutic relevance, particularly for HIV and possibly for CMV. For the non-HIV infections, the diagnostic criteria remain to be established, with the clinical role of immunostaining and *in situ* hybridization not part of routine pathologic practice. For these infections, the evidence base linking these viruses to collapsing glomerulopathy deserves further systematic investigation. Further work should also address the molecular mechanisms of glomerular cell injury and the role of host responses, including the role of host genetic susceptibility.

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(See related article by Grover *et al.* Cytomegalovirus-induced collapsing focal segmental glomerulosclerosis. *Clin Kidney J* 2013; 6: 71–73)

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