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Association of parvovirus B19 infection with idiopathic collapsing glomerulopathy

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Association of parvovirus B19 infection with idiopathic collapsing glomerulopathy.

Background. Collapsing glomerulopathy (CG), a disorder with severe glomerular and tubular involvement, occurs either as an idiopathic lesion or in some patients with human immunodeficiency virus (HIV) infection known as HIV-associated nephropathy (HIVAN). We previously reported a renal transplant recipient with de novo CG and red cell aplasia in association with persistent parvovirus B19 (PVB19) infection. This prompted us to look for an association between PVB19 infection and CG.

Methods. DNA from archived biopsies of patients with CG was analyzed for PVB19 by polymerase chain reaction (PCR). Results were compared with HIVAN, idiopathic focal segmental glomerulosclerosis (FSGS), and controls. In situ hybridization (ISH) was done to localize PVB19 in renal biopsies. Peripheral blood specimens of patients with CG, HIV infection, healthy controls, and randomly selected hospitalized patients (sick controls) were also analyzed for PVB19.

Results. PVB19 DNA was detected in renal biopsies of 18 out of 23 (78.3%) patients with CG, 3 out of 19 (15.8%) with HIVAN, 6 out of 27 (22.2%) with FSGS, and 7 out of 27 (25.9%) controls ($P < 0.01$, CG vs. HIVAN, FSGS, and controls). PVB19 was detected in peripheral blood of 7 out of 8 (87.5%) CG patients, 3 out of 22 (13.6%) with HIV infection, 4 out of 133 (3%) healthy controls, and 2 out of 50 (4%) sick controls ($P < 0.001$, CG vs. HIV infected, healthy, and sick controls). PVB19 was identified in glomerular parietal and visceral epithelial and tubular cells by ISH.

Conclusions. The significantly higher prevalence of PVB19 DNA in renal biopsies and peripheral blood of CG patients suggests a specific association between PVB19 infection and CG. In susceptible individuals, renal epithelial cell infection with PVB19 may induce CG.

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Collapsing glomerulopathy (CG) is a distinct variant of focal and segmental glomerulosclerosis (FSGS) that may occur as an idiopathic process or in patients infected with human immunodeficiency virus (HIV) known as HIV-associated nephropathy (HIVAN) [1–5]. Patients with idiopathic CG and HIVAN share similar clinical and pathologic features with most cases rapidly progressing to end-stage renal disease (ESRD) [1, 4]. The etiology and pathogenesis of these disorders are unknown. There is evidence suggesting that HIV infection of renal epithelial cells may be responsible for inducing HIVAN [6–8]. Recently, we reported de novo CG in an HIV-negative renal transplant recipient with chronic PVB19 infection [9]. PVB19 DNA was detected in blood and renal tissue. These findings in a patient with ESRD secondary to autosomal dominant polycystic disease suggested a causal relationship between PVB19 infection and CG.

PVB19 infection is common in the general population, with increasing prevalence with age [10]. Although most infections are minimally symptomatic, aplastic anemia can occur in patients with sickle cell disease and other chronic hemolytic disorders infected with PVB19 [11, 12]. Infection may become chronic in immunosuppressed individuals and cause pure red cell aplasia [13, 14]. Focal segmental glomerulonephritis and FSGS were described in children with sickle cell disease and PVB19 infection [15, 16]. Recently, a greater prevalence of PVB19 DNA was reported in renal biopsies of patients with idiopathic and collapsing forms of FSGS as compared with those with membranous nephropathy and minimal change disease [17]. Based on our observations [9] and those of others [15–17], we speculated that PVB19 infection might induce CG or other form of glomerulopathies in susceptible individuals. To test this hypothesis, we studied archived renal biopsies of patients with CG, HIVAN, and FSGS, and controls for PVB19 DNA by polymerase chain reaction (PCR). Additionally, we prospectively analyzed peripheral blood specimens of patients with CG, those infected with HIV, healthy volunteers (controls),

and randomly selected hospitalized patients (sick controls) for PVB19.

METHODS

Renal biopsy specimens

Renal biopsies accessioned in the renal pathology division at Cedars-Sinai Medical Center (Los Angeles, CA, USA) between January 1994 to March 1999 were utilized. The specimens were processed in the standard fashion and evaluated by light, immunofluorescence and electron microscopies [18]. Frozen renal tissue from patients with CG ($N = 23$), HIVAN ($N = 19$), idiopathic FSGS ($N = 27$), and controls (normal biopsies of patients with hematuria, minimal change disease, thin basement membrane disease, and normal portion of nephrectomies for renal cell carcinoma, $N = 27$) were examined for PVB19 DNA.

Peripheral blood specimens

Peripheral blood specimens in ethylenediaminetetraacetic acid (EDTA) were collected prospectively from 8 patients with CG, 22 patients with HIV infection, 13 controls, and 50 sick controls. Renal biopsy specimens were available for PVB19 DNA analysis in all patients with CG, whereas none with HIV infection, controls, or sick controls had renal biopsies. Leukocyte pellets were prepared by lysing erythrocytes with ammonium chloride and ammonium bicarbonate and submitted for DNA extraction [19]. Additionally, serum specimens were obtained from 120 blood bank donors.

DNA extraction

DNA was extracted from renal tissue and leukocyte pellets using QIAamp tissues kit (Qiagen Inc., Chatsworth, CA, USA). Briefly, proteinase K stock solution was added to five or six (4 μ thick) renal tissue sections or to leukocyte pellets to break off all cell membranes and release nucleic acid in the solution. DNA was precipitated by adding 100% ethanol. Five micrograms of t-RNA were added to facilitate DNA precipitation from tissue sections before adding ethanol. This mixture was then passed through spin columns and filtrate discarded. Spin columns were washed twice. DNA bound to spin columns was eluted with 50 μL of Tris-EDTA (TE; 1 mol/L, 0.1 mmol/L) for tissue sections and 100 μL of TE for leukocyte pellets. The DNA concentration was calculated by measuring optical density at 260 nm in solutions obtained from leukocyte pellets. DNA thus obtained was stored at −80°C until analyzed. One microgram of DNA from leukocyte pellets or 5 μL DNA solution from tissue sections were submitted for PCR.

Gene amplification by PCR

Table 1 shows the sequence of primers, product size, and number of cycles used for PCR. DNA extracted from tissue and blood was analyzed for insulin and β-globin, respectively, to assess its adequacy.

PVB19-PCR. Nested PCR was used to detect PVB19 DNA. Two sets of primers targeted at two separate genes, one encoding nonstructural (PVB19-a) and the other nucleocapsid (PVB19-b) region of PVB19, were used (Table 1).

(a) "Outer" PCR. Five microliters or 1 μg of DNA solution in TE extracted from the renal biopsy and blood, respectively, or 5 μL of serum were mixed with 20 μL of mixture containing 5.0 mmol/L of magnesium chloride, 0.2 mmol/L dNTP (Boeringer Mannheim, Indianapolis, IN, USA), 0.1 μmol/L each of upstream and downstream primers (Oligos ETC., Wilsonville, OR, USA), 1 unit of Amplitaq (Perkin Elmer Cetus, Norwalk, CT, USA), 1 × PCR buffer (Perkin Elmer), and sterile water (Life Technologies, Gaithersburg, MD, USA). PCR was performed in a thermal cycler (Perkin-Elmer) programmed for two minutes at 95°C followed by a cycle of 30 seconds at 95°C, 30 seconds at 60°C, and 30 seconds at 72°C for 30 cycles, followed by cooling to 4°C.

(b) "Nested" PCR. Four microliters of outer PCR product were mixed with 21 μL of mixture containing 2.0 mmol/L of magnesium, 0.5 μmol/L each of upstream and downstream primers, and the remaining reagents in same amount as in the outer PCR and amplified for 25 cycles. A known positive control (PVB19 DNA) and a negative control (water) were included. The PCR products were run through 5% polyacrylamide gel to separate and size DNA fragments. The gel was stained with ethidium bromide and analyzed under ultraviolet light.

Insulin-polymerase chain reaction. Insulin-PCR conditions were same as that for PVB19 except for the following differences. In the outer PCR, the magnesium chloride concentration was 3.0 mmol/L, and upstream and downstream primers were 0.1 μmol/L each. Amplification was done for 15 cycles. In the nested PCR, 2 μL of outer PCR product were mixed with 23 μL of mixture containing 3.0 mmol/L magnesium chloride and 0.7 μmol/L each of upstream and downstream primers and were amplified for 20 cycles.

β-Globin-polymerase chain reaction. Single PCR was used for β-globin as previously published [20].

All possible precautions were taken to avoid cross contamination while cutting the sections, at the time of DNA extraction, and during PCR procedures. Cryostat was cleaned meticulously with bleach after cutting sections from each specimen. Designated pipettes and filtered pipette tips were used for DNA extraction and PCR. All reagents were aliquoted. Different laboratory benches were used for pre- and post-PCR procedures.

Table 1. Primers and experimental conditions for polymerase chain reaction (PCR)

Target gene	Primer sequence	Product *bp*	Amplification cycles	Reference
PV B19-a[a]				
Outer	5′-AAT ACA CTG TGG TTT TAT GGG CCG 3′-CCA TTG CTG GTT ATA ACC ACA GGT	284	30	[37]
Nest	5′-AAT GAA AAC TTT CCA TTT AAT GAT GTAG 3′-CTA AAA TGG CTT TTG CAG CTT CTAC	103	25	
PVB19-b[b]				
Outer	5′-AAG TTT GCC GGA AGT TCC CG 3′-AGC ATC AGG AGC TAT ACT TCC	403	30	[38]
Nest	5′-CCC AAG CAT GAC TTC AG 3′-TCT AAA TAT CTC CAT GG	279	25	
Insulin[c]				
Outer	5′-GGA CAG GCT GCA TCA GAA GAG G 3′-GGT CTT GGG TGT GTA GAA GAA GC	391	15	
Nest	5′-ATC AAG CAG GTC TGT TCC AAG G 3′-CAC ACT AGG TAG AGA GCT TCC A	333	20	
β-globin	5′-TTG CTA ATC ATG TTC ATA CC 3′-AGC AAG AAA GCG AGC TTA GT	184	35	[20]

[a] PV B19-a and [b] PVB19-b, targeted at genes encoding nonstructural and nucleocapsid regions, respectively
[c] Insulin, designed in our laboratory

The PCR amplification was performed twice on each DNA extract. In 12 out of 33 (36%) biopsy specimens that were positive for PVB19 DNA, repeat biopsy sections were obtained for DNA extraction and subsequent PCR analysis to confirm results. These 12 specimens were obtained from those in which enough biopsy material was available.

In situ hybridization for PVB19

Biotinylated probe for PVB19. Plasmid containing PVB19 DNA was the courtesy of Dr. P. Tattersall [21]. The plasmid was transformed in *Escherichia coli*, INVαF cells (Invitrogen Co., San Diego, CA, USA). After colonies were cultured, the plasmid was isolated by miniprep DNA purification system (Promega, Madison, WI, USA). The plasmid was confirmed by fragment size obtained after digestion with restriction enzyme and by PCR. The digested plasmid was separated on an agarose gel, and a 3.9 kb fragment was excised and isolated using quick gel extraction kit (Qiagen). PVB19 DNA thus obtained was biotinylated using BioPrime DNA labeling system (GIBCO BRL, Grand Island, NY, USA).

In situ hybridization. A biotinylated probe was used for in situ detection of PVB19 DNA by the Enzo pathoGene DNA probe assay protocol (Enzo Diagnostics, Inc., Farmingdale, NY, USA) [22]. Slides containing one to three sections were deparaffinized, dehydrated, and postfixed in neutral-buffered formalin for 20 minutes. After rinsing, slides were treated with pronase for three minutes and were rinsed and subsequently fixed in paraformaldehyde for five minutes. After treatment with glycine and dehydration, the biotin-labeled probe was applied overnight. Streptavidin alkaline phosphatase (BRL) was added followed by NBT/BICP developer used overnight at 4°C. Slides were counterstained with methyl green. Bone marrow slides from two fetuses with PVB19 induced hydrops fetalis were used as positive controls. Negative controls included pretreatment with DNase, and substitution of PVB19 probe with cytomegalovirus, and Epstein-Barr virus probes.

Ultrastructural examination of renal specimens for PVB19

Three biopsies with CG and positive in situ hybridization (ISH) for PVB19 were selected for ultrastructural evaluation. Three to five glomeruli with large numbers of vacuolated atypical visceral epithelial cells were examined for PVB19 virions.

Clinical data and statistical analysis

Clinical information was obtained by retrospective chart review. Mann–Whitney *U* test was used for statistical comparison of ages between various groups. Chi-square test was used for the remaining comparisons.

RESULTS

Demographics and clinical information are shown in Table 2. The mean age of CG patients was comparable to HIVAN, FSGS, and controls. There were more female patients in CG compared with HIVAN and FSGS. CG and HIVAN patients were predominantly African Americans. Hypertension, hematuria, proteinuria, and nephrotic syndrome were observed in all groups. Elevated creatinine and anemia were more frequent in CG and HIVAN patients.

Table 2. Demographics and clinical information

	CG	HIVAN	FSGS	Control
Number of patients	23	19	27	27
Age (mean ± SD)	39.7 ± 17	36.6 ± 12	45.7 ± 23	30 ± 14
Sex *M*:*F*	9:14[a,b]	14:5	18:9	11:16
Race				
African Americans %	16 (72.7)[b,c]	17 (94.1)	2 (7.4)	3 (11.1)
Caucasian/Hispanic/Other	2/3/2	1/0/1	16/7/2	12/9/3
Clinical features %				
Proteinuria	23 (100)	19 (100)	27 (100)	N/A
Nephrotic syndrome	17 (73.9)	15 (78.9)	17 (62.9)	
Hematuria	18 (78.2)	15 (78.9)	14 (51.8)	
Hypertension	14 (60.8)	10 (52.6)	10 (37)	
Elevated creatinine	22 (95.6)[b]	18 (94.7)	13 (48.1)	
Anemia	8 (34.8)[b]	12 (63.1)	2 (7.4)	

Abbreviations are: CG, collapsing glomerulopathy; HIVAN, HIV-associated nephropathy; FSGS, focal segmental glomerulosclersis.
[a,b,c]$P < 0.05$, CG vs. HIVAN, CG vs. FSGS and CG vs. control, respectively

Table 3. PVB19 DNA detection in renal specimens by PCR

Diagnosis	Sample *N*	PVB19 DNA (+) *N* (%)
CG	23	18 (78.3)[a]
HIVAN	19	3 (15.7)
FSGS	27	6 (22.2)
Controls	27	7 (25.9)

[a]$P < 0.01$, CG vs. HIVAN, FSGS and controls

Table 4. PVB19 DNA detection in the peripheral blood by PCR

Diagnosis	Sample *N*	PVB19 DNA (+) *N* (%)
CG	8[c]	7 (87.5)[a]
HIV (+)	22	3 (13.7)
Controls[b]	133	4 (3)
Sick controls	50	2 (4)

[a]$P < 0.001$, CG vs. HIV (+), controls and sick controls
[b] Controls included leukocytes from 13 and serum specimens from 120 healthy individuals
[c] PVB19 DNA results in the blood specimens of these patients corresponded with the biopsy results

PVB19 DNA detection in renal biopsy specimens

Ninety-six specimens were available, 23 CG, 19 HIVAN, 27 FSGS, and 27 controls. Insulin gene was detected in all of them. PVB19 DNA was detected in 18 out of 23 CG (78.3%), which was significantly higher ($P < 0.01$) than HIVAN (15.8%), FSGS (22.2%), and controls (25.9%). No significant differences were observed between HIVAN, FSGS, and controls (Table 3). PVB19 DNA was detected in 12 of 16 African American patients (75%) and 6 of 7 (85.7%) in non–African Americans with CG (P = NS). There were only two black patients in the FSGS group, and PVB19 DNA was detected in both as compared with 4 out of 25 nonblacks (16%).

PVB19 DNA detection in the peripheral blood

β-Globin was detected in all samples. PVB19 DNA was detected in the peripheral blood of 7 out of 8 CG patients (87.5%; Table 4), which was significantly higher ($P < 0.001$) than those with HIV infection (13.7%) and controls (3%), and sick controls (4%). PVB19 DNA results in blood of patients with CG exactly corresponded with renal biopsy results. In two patients with CG and blood samples obtained at monthly intervals, PVB19 DNA was identified until six and nine months after the initial diagnosis. It could no longer be detected following treatment with intravenous immune globulin and significant reduction in immunosuppression.

PVB19 DNA localization in renal biopsies

Of 13 biopsy specimens (5 CG, 4 FSGS, 3 HIVAN, and 1 control) positive for PVB19 DNA by PCR, PVB19 was detected in 10 by ISH (Table 5). PVB19 DNA was present in some glomerular visceral epithelial cells in nine, parietal epithelial cells in eight, and tubular cells in seven (Fig. 1 A, C, and F). In positive CG and HIVAN cases, all visceral epithelial cells containing PVB19 genome were morphologically abnormal, with the percentage of positive cells usually ranging from 10 to 40% and in occasional case as high as 80% for each glomerulus (Fig. 1C). Positive parietal cells were morphologically normal or had expanded cytoplasm, which contained small vacuoles (Fig. 1A), and were always in glomeruli with at least segmental collapsing features. Positive epithelial cells in FSGS glomeruli were infrequent and overlay the sclerotic segments. Tubular epithelium containing the PVB19 genome was always in tubules of normal size, usually without inflammation, and varied from one or two positive tubules to 30% involvement; microcystically dilated tubules were virtually always negative. Localization of PVB19 to renal epithelium was identical in patients with CG, FSGS, and HIVAN, although staining was somewhat less apparent in the latter two groups. PVB19 DNA was detected primarily in the cytoplasm

Table 5. Number of cases with PVB19 detected by *in situ* hybridization

	PVB19 DNA +		PVB19 DNA −		
Diagnosis	PCR	In situ	PCR	In situ	PVB19 DNA localization
CG	(5)	(5)	(4)	(4)	PEC (4), VEC (4), TC (3), AEC (1)
HIVAN	(3)	(2)	(2)	(2)	PEC (2), VEC (2), TC (1)
FSGS	(4)	(3)	(4)	(4)	PEC (2), VEC (3), TC (3)
Controls	(1)	(0)	(3)	(0)	

Abbreviations are: PEC, parietal epithelial cells; VEC, visceral epithelial cells; TC, tubular cells; AEC, arterial endothelial cells.

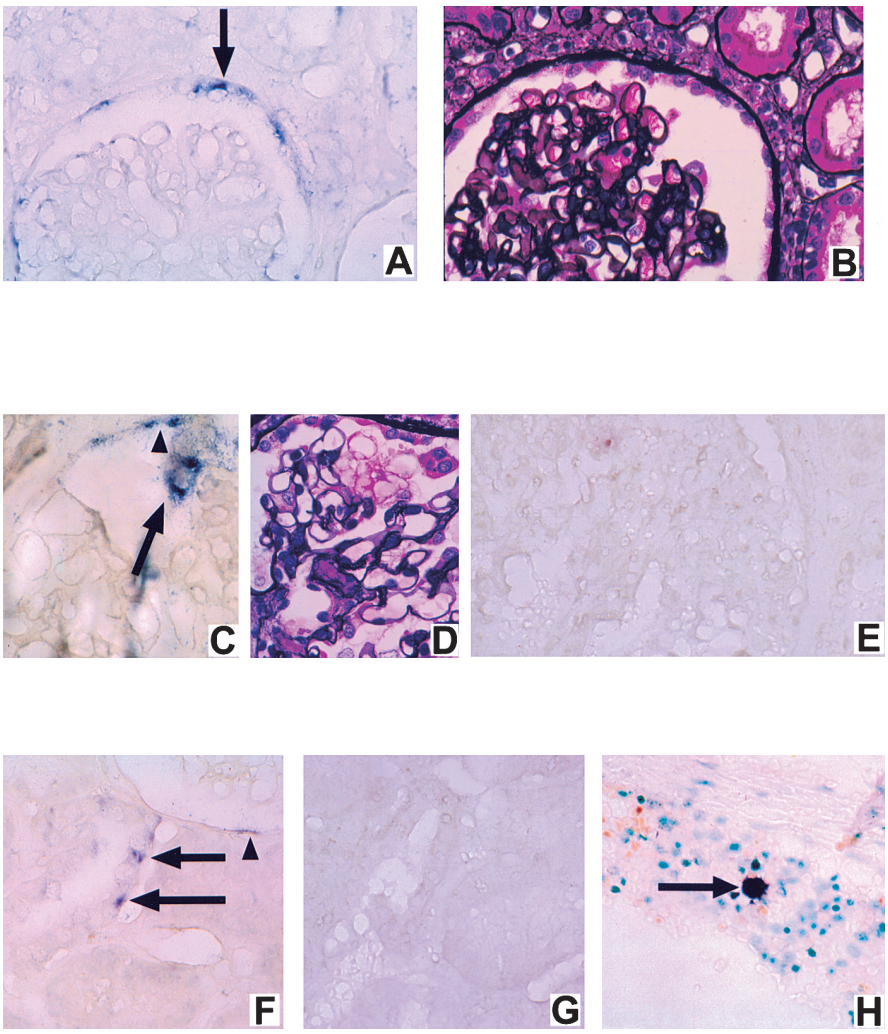

Fig. 1. Parvovirus B19 (PVB19) in situ hybridization of renal biopsy from patient with collapsing glomerulopathy (CG) and PVB19 (+) by polymerase chain reaction (PCR). Viral genome in (*A*) parietal epithelial cells (arrow) of otherwise normal-appearing glomerulus; (*C*) enlarged glomerular epithelial cell (arrow) overlying collapsed segment, and adjacent parietal epithelium (arrowhead); (*F*) tubular epithelial cell cytoplasm (arrows) with weak staining of glomerular parietal epithelium (arrowhead). (*B* and *D*) Compare with periodic acid methanamine silver-stained sections. (*E* and *G*) Negative controls pretreated with DNase. (*H*) Positive control showing staining of early erythroid line cell (arrow) in bone marrow from a PVB19 infected fetus. Original magnification ×160.

of renal epithelial cells, but a perinuclear distribution cannot be excluded (Fig. 1C). Of 13 specimens negative for PVB19 by PCR, none were positive by in situ. In the bone marrow of fetuses with hydrops fetalis, intense staining for PVB19 was seen in the nuclei of early erythroid cells (Fig. 1H).

Electron microscopy

Electron microscopy of three biopsies positive by ISH for PVB19 did not reveal viral particles in the cytoplasm or nuclei of any cells.

DISCUSSION

In many patients with CG, a history of preceding or concurrent systemic illness suggests an infectious etiology [1, 2], but no specific infections have been identified. This report demonstrates an association between PVB19 infection and CG. PVB19 DNA was detected in 78% of renal biopsies from patients with CG, a number significantly greater than controls, HIVAN, and FSGS. Although patients with CG and HIVAN shared similar demographic, clinical, and many pathologic features, the

prevalence of PVB19 was not increased in HIVAN, suggesting that PVB19 infection is specific to the subgroup of CG. This is further supported by isolation of PVB19 DNA from the peripheral blood of 87% CG patients compared with 13.7% with HIV infection, 3% of healthy controls, and 4% of sick controls. There was an increase in frequency of PVB19 detection from the peripheral blood of HIV infected individuals as compared with controls ($P < 0.05$), but this was not associated with increased PVB19 isolation in renal biopsies from HIVAN patients.

An association of PVB19 infection with focal proliferative glomerulonephritis and FSGS was described in seven patients with sickle cell anemia and PVB19-induced aplastic crisis [16]. However, our close review of the published biopsy photographs suggests the lesion to be CG. Several investigators have reported an increased incidence of de novo CG in transplant recipients in recent years [23, 24]. This may be due to increased use of powerful immunosuppression and therefore an increased incidence of viral infections, but association with specific viral agents has not been sought. Based on our data, we speculate that CG in transplant recipients may be related, at least in part, to PVB19 infection.

While this manuscript was in preparation, Tanawattancharoen et al reported their findings in a similar study [17]. They found PVB19 DNA in 90% of patients with idiopathic CG, a number similar to that of ours. However, they detected PVB19 in 80% with idiopathic FSGS and 54% controls in contrast to 22 and 26%, respectively, in our series. The reason for these discrepancies is unclear and may be related to regional and ethnic variations. A study of PVB19 DNA in renal biopsies of HIVAN patients as well as the information on prevalence of PVB19 DNA in the peripheral blood of CG and control population from their region would have been helpful to explain some of these differences.

In this study, viral genome was identified within renal epithelial cells in 10 of 13 biopsy specimens positive for PVB19 by PCR (Table 5). This confirmed the PCR findings and excluded the possibility that detection of PVB19 in renal tissue was due to contamination by PVB19-positive blood or cross contamination by other positive samples. The inability to detect PVB19 by ISH in the remaining three specimens may be due to low viral copy number and focal infection; these features may also explain the lack of virion identification ultrastructurally. Localization of PVB19 to glomerular parietal and visceral and tubular epithelial cells demonstrates the capability of virus to infect renal epithelium. PVB19 binds to a globoside (Gb 4) receptor on erythrocytes [25]. Recently, Cooling, Koerner, and Naides demonstrated Gb 4 receptors in several tissues, including human kidney [26]. Although specific intrarenal sites of this receptor are unknown, it is possible that epithelial cells express Gb 4 receptors rendering them susceptible to PVB19 infection. Further studies are needed to identify renal cells capable of expressing Gb 4 receptor.

Parvovirus B19 is localized primarily to the nucleus of infected erythrocyte pronormoblasts [27]. The apparent cytoplasmic distribution of PVB19 in the renal epithelial cells by in situ may be related to the unique characteristics of these cells. It has been shown that uptake of the parvoviruses occurs irrespective of the host cell position in the mitotic cycle, allowing parvoviruses to infect resting and proliferating cells with equal efficiency [28, 29]. Whether PVB19 goes through a productive phase and initiates pathogenic changes in these renal epithelial cells cannot be addressed by this study. However, the cytoplasmic changes observed in these cells positive for PVB19 suggests the pathogenecity of the virus.

The pathogenesis of CG remains elusive. The characteristic glomerular changes include increased size and number of glomerular visceral epithelial cells that contain cytoplasmic vacuoles, protein reabsorption droplets, and occasional mitotic figures [30], suggesting these cells play a prominent role in disease development [31]. Recently, it has been suggested that parietal epithelial cells also are involved in this process [32]. We detected PVB19 genome in both parietal and visceral epithelial cells, the cells implicated in the pathogenesis of CG, suggesting that both cell types interact with the virus. In HIVAN, HIV has been identified in similar locations by ISH [33, 34]. Our observations and these studies suggest that renal epithelial cell infection by PVB19 or HIV may initiate CG or HIVAN, respectively.

Since PVB19 infection is common in the general population but CG is a rare entity, we speculate that the renal response to PVB19 depends on several viral, host, or other cofactors. The prevalence of PVB19 DNA in 26% biopsy specimens of control population by PCR also suggests that an additional factor/insult is needed to cause pathogenic effects. Of eight CG patients studied prospectively in this series, seven had PVB19 DNA detected in the blood at the time of renal biopsy. In two patients, PVB19 was detected for six and nine months. This suggests that some patients have specific immune defects resulting in an inability to generate cellular and humoral immune responses required to clear the virus, and leads to viral persistence with presumed increased infectivity and additional clinical and/or disease manifestations. African ancestry appears to be an important risk factor, as CG and HIVAN occur predominantly in this population [1, 4]. Recent data have shown that African Americans are hyperproducers of transforming growth factor-β, a cytokine associated with a profibrogenic profile [35]. It is possible this patient cohort has an excessive proliferative and sclerosing response to a viral insult (HIV or PVB19). Alternatively, PVB19 receptor density on erythrocytes and renal epithelium may be different

in individuals with different genetic backgrounds. It is possible those lacking Gb 4 receptors cannot be infected with PVB19 in the kidney, indicating individual variation in susceptibility to PVB19 infection [36].

In conclusion, we have shown a significant association of the PVB19 genome in renal tissue and peripheral blood with CG. PVB19 infects renal epithelial cells and may initiate CG in susceptible individuals. However, most people with PVB19 infection do not have and likely will never develop CG. Further studies are needed to identify factors rendering susceptibility to the development of CG, to identify renal cells that express PVB19 receptors, to demonstrate pathogenic effects of the virus on renal epithelium, and to understand defects in immune responses to PVB19 infection in CG patients. These would be critical to unraveling the pathogenesis of PVB19 associated CG and for developing novel therapeutic approaches to this disease.

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APPENDIX

Abbreviations used in this article are: BRL, streptavidin alkaline phosphatase; CG, collapsing glomerulopathy; EDTA, ethylenediaminetetraacetic acid; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; HIV, human immunodeficiency virus; HIVAN, human immunodeficiency virus-associated nephropathy; ISH, in situ hybridization; PCR, polymerase chain reaction; PVB19, parvovirus B19; TE, Tris-EDTA; TGF-β, transforming growth factor-β.

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